# Childhood Vitamin D Deficiency in the UK: Diagnosis, Clinical Consequences, and Healthcare Costs

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PhD Thesis

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2017

# Declaration

I, Emre Basatemur, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed _____

# Abstract

**Background:** Vitamin D has attracted considerable academic and clinical attention over the last two decades. However, the epidemiology of symptomatic vitamin D deficiency in UK children is poorly characterised, and the impact of the recent interest on paediatric clinical practice has not been explored.

**Methods:** A systematic review of the global incidence of symptomatic vitamin D deficiency in children was undertaken. A prospective surveillance study was conducted across the UK and Ireland to determine the incidence of hypocalcaemic seizures secondary to vitamin D deficiency in children. Cohort studies were undertaken to examine temporal trends in the diagnosis of vitamin D deficiency among children in clinical practice in the UK, and investigate healthcare expenditure related to vitamin D testing and prescribing in primary care.

**Results:** Four higher quality studies, from high-income countries with predominantly Caucasian populations, provided a pooled annual incidence estimate for symptomatic vitamin D deficiency of 3.4 per 100,000 children. The annual incidence of hypocalcaemic seizures secondary to vitamin D deficiency in the UK and Ireland was 3.5 per million children aged 0-15 years, with male infants from South Asian and black ethnic backgrounds at greatest risk. There was a 15-fold increase in the diagnosis of vitamin D deficiency among children in UK clinical practice between 2008-2014. Older age (≥10 years), non-white ethnicity, and social deprivation were associated with higher rates of diagnosis. Healthcare expenditure on vitamin D tests and prescriptions for children in primary care increased 13-fold between 2008-2014, with national costs in England estimated at £4.3 million in 2014.

**Conclusion:** Considered in the context of the existing literature, these studies suggest that vitamin D deficiency may be over-tested and over-diagnosed, yet under-prevented, among children in the UK. These findings have implications for public health policy, clinical practice and health service delivery, and inform areas for future research.

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# Abbreviations

| | |
|---|---|
| **25-OH-D** | 25-hydroxyvitamin D |
| **ACOG** | American College of Obstetricians and Gynecologists |
| **ACU** | Acceptable computer usage |
| **AHD** | Additional health data |
| **ALP** | Alkaline phosphatase |
| **AMR** | Acceptable mortality recording |
| **A&E** | Accident and emergency |
| **BCa** | Bias-corrected and accelerated |
| **BNF** | British National Formulary |
| **BNFc** | British National Formulary for Children |
| **BPSU** | British Paediatric Surveillance Unit |
| **$Ca^{2+}$** | Calcium |
| **CAG** | Confidentiality Advisory Group |
| **CDC** | Centers for Disease Control and Prevention |
| **CI** | Confidence interval |
| **Co. $Ca^{2+}$** | Corrected calcium |
| **CSDMRUK** | Cegedim Strategic Data Medical Research UK |
| **CSO** | Central Statistics Office, Ireland |
| **DEFRA** | Department for Environment, Food & Rural Affairs |
| **DoH** | Department of Health |
| **EDD** | Estimated date of delivery |
| **GI** | Gastrointestinal |
| **GP** | General practitioner |
| **HES** | Hospital Episode Statistics |
| **HSCIC** | Health and Social Care Information Centre |
| **ICD** | International Classification of Diseases |
| **ICER** | Incremental cost-effectiveness ratio |
| **IMD** | Index of Multiple Deprivation |
| **IOM** | Institute of Medicine |
| **IQR** | Interquartile range |
| **IU** | International Units |
| **LMIC** | Low- and middle-income countries |
| **LMP** | Last menstrual period |
| **LRT** | Likelihood ratio test |
| **MOB** | Month of birth |
| **ng/ml** | Nanograms per millilitre |

| | |
|---|---|
| **NHS** | National Health Service |
| **NIC** | Net ingredient cost |
| **NIC/Qty** | Net ingredient cost per quantity of drug |
| **NICE** | National Institute for Health and Care Excellence |
| **NIGB** | National Information Governance Board for Health and Social Care |
| **nmol/l** | Nanomoles per litre |
| **NRS** | National Records of Scotland |
| **ODPM** | Office of the Deputy Prime Minister |
| **ONS** | Office for National Statistics |
| **PCA** | Prescription Cost Analysis |
| **PHE** | Public Health England |
| **PTH** | Parathyroid hormone |
| **PYAR** | Person-years at risk |
| **QALY** | Quality-adjusted life year |
| **RCPCH** | Royal College of Paediatrics and Child Health |
| **RCT** | Randomised controlled trial |
| **RR** | Rate ratio |
| **SACN** | Scientific Advisory Committee on Nutrition |
| **SHA** | Strategic health authority |
| **SD** | Standard deviation |
| **THIN** | The Health Improvement Network |
| **UK** | United Kingdom |
| **US** | United States |
| **UCLH** | University College London Hospitals NHS Trust |
| **VDD** | Vitamin D deficiency |
| **YOB** | Year of birth |

# Acknowledgements

I principally wish to thank my supervisors Professor Alastair Sutcliffe, Dr Greta Rait, and Dr Laura Horsfall for their guidance, support, and patience. I am particularly grateful to Alastair for his guidance in the conception and design of the projects, and his unwavering support in guiding my professional development. I am particularly grateful to Greta for her encouragement, guidance with the study methodology, and her keen eye for detail.

I wish to thank Dr Louise Marston for providing statistical advice for the work undertaken using The Health Improvement Network (THIN) database, and Rachael Hunter for her health economics guidance.

I thank all paediatricians in the UK and Ireland who reported cases for the British Paediatric Surveillance Unit (BPSU) study, and took the time to complete and return the study questionnaire. I acknowledge the BPSU staff at the Royal College of Paediatrics and Child Health (RCPCH) for facilitating the data collection. In particular, I wish to thank Richard Lynn, Dr Rachel Knowles, Helen Friend, and Rachel Winch for their assistance during the planning and data collection stages of the study.

I am grateful to the RCPCH for funding the BPSU study through the Sir Peter Tizard Bursary, and I am grateful to the National Institute for Health Research (NIHR) for funding the THIN project through a Doctoral Research Fellowship. This work would not have been possible without the financial support from these organisations.

Finally, and most importantly, I am incredibly grateful for the love and support of Gemma, Ayla, and my mother. I thank them for their patience and understanding whilst I have been writing this thesis.

# Chapter 1

# Introduction

## 1.1 Introduction

Vitamin D plays an important role in bone metabolism and calcium homeostasis, and its deficiency can cause various clinical complications in children including rickets and hypocalcaemia. Vitamin D has attracted considerable clinical and academic interest over the last two decades. In relation to child health, there are concerns that clinical complications of vitamin D deficiency have increased in frequency among children in high-income countries such as the UK, USA, and Australia (Ahmed et al, 2011; Allgrove, 2004; Holick, 2006; Robinson et al, 2006; Shaw & Pal, 2002). In the UK, this has generated criticism of national public health policy regarding the prevention of vitamin D deficiency (Davies & Shaw, 2011; Högler, 2015; Hyppönen & Boucher, 2010), and prompted the Department of Health to commission a review of the Healthy Start vitamin programme (Lemer, 2013; NICE, 2015). However, these concerns have largely been based upon anecdotal reports and local case series, and quantitative evaluation of the epidemiology of symptomatic vitamin D deficiency has been limited.

There has also been considerable debate and controversy regarding the possibility that vitamin D may have clinically relevant physiological activity beyond its established role in calcium and bone metabolism, and that vitamin D deficiency *may* increase the risk of various non-musculoskeletal diseases (SACN, 2016; Theodoratou et al, 2014). As vitamin D has attracted increasing attention, large increases in vitamin D testing and prescribing have been reported in adult practice over the last decade, with significant associated healthcare costs (Bilinski & Boyages, 2012; 2013; HSCIC, 2005; 2015b). However, the influence of the increased interest in vitamin D on paediatric clinical practice has not been explored.

## 1.2 Aims and Objectives

The overall aims of this research were to investigate the epidemiology of symptomatic vitamin D deficiency in children, explore temporal trends in the diagnosis of vitamin D deficiency in clinical practice, and examine healthcare expenditure related to vitamin D testing and prescribing in children.

The main research objectives were:

1. To systematically review the published literature on the incidence of symptomatic vitamin D deficiency in children worldwide.

2. To estimate the incidence of hypocalcaemic seizures secondary to vitamin D deficiency in children in the UK and Ireland, both overall and stratified for demographic characteristics.

3. To describe the clinical characteristics, biochemical profile, clinical management, and clinical outcomes in children who develop hypocalcaemic seizures secondary to vitamin D deficiency.

4. To determine rates of diagnosis of vitamin D deficiency among children in UK clinical practice between 2000 and 2014, and examine differences in diagnosis by socio-demographic characteristics.

5. To examine the recording of symptoms, in primary care health records, among children diagnosed with vitamin D deficiency.

6. To estimate healthcare costs arising from vitamin D testing and prescribing in primary care for children in the UK.

## 1.3 Outline of the Thesis

The subsequent chapters contained in this thesis are summarised below:

**Chapter 2:** This background chapter summarises current understanding regarding the influence of vitamin D on children's health, from a UK perspective.

**Chapter 3:** This chapter describes a systematic literature review undertaken to explore the incidence of symptomatic vitamin D deficiency in children worldwide, and investigate differences in incidence by demographic factors.

**Chapter 4:** This chapter describes a prospective surveillance study undertaken across the UK and Ireland, using the British Paediatric Surveillance Unit reporting system, investigating the incidence of hypocalcaemic seizures secondary to vitamin D deficiency in children.

**Chapter 5:** This chapter describes a cohort study, using electronic healthcare records from UK primary care held in The Health Improvement Network (THIN) database, which examines longitudinal trends in the diagnosis of vitamin D deficiency in children, and explores differences in diagnosis by socio-demographic factors.

**Chapter 6:** This chapter describes a cohort study, using the THIN primary care database, which examines longitudinal trends in healthcare expenditure arising from vitamin D testing and prescribing in children in primary care.

**Chapter 7:** In the discussion chapter, the main findings from the work described in chapters 3 to 6 are summarised, the implications of these research findings for clinical practice and public health policy are discussed, and recommendations for future research are made.

## Chapter 2

# Background: Vitamin D in Relation to Child Health in the UK

## 2.1 Introduction

This chapter summarises the state of current understanding regarding vitamin D biology and the influence of vitamin D on children's health, from a UK perspective.

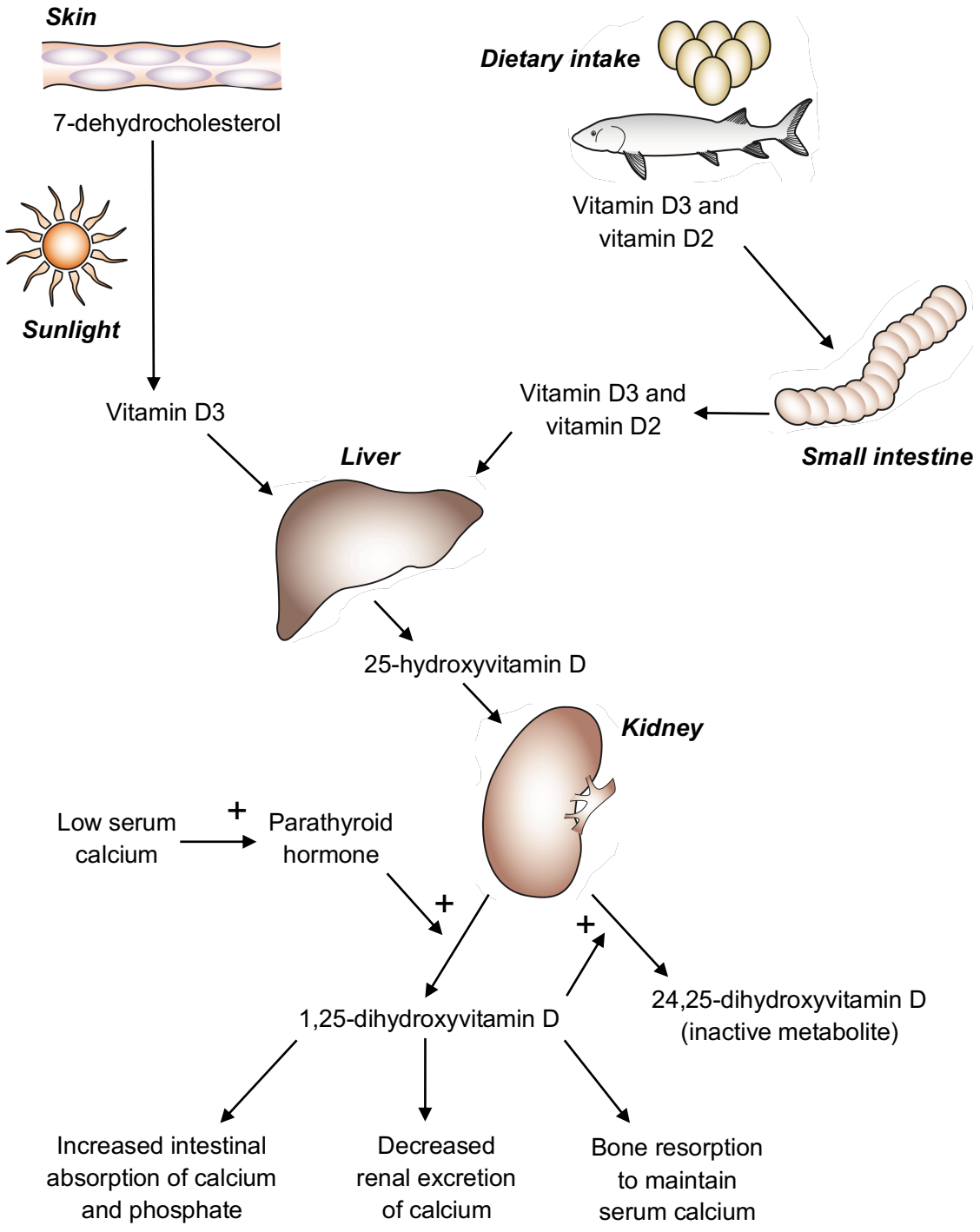
## 2.2 Vitamin D Biology

The term vitamin D refers to a group of secosteroid compounds (organic compounds that are structurally related to steroids with a cleavage in one of the four carbon atom rings) that are precursors of the active hormone 1,25-dihydroxyvitamin D, which plays an important role in bone metabolism and calcium homeostasis (Allgrove, 2015). Vitamin D exists in two main forms: vitamin D3 (colecalciferol) and vitamin D2 (ergocalciferol). They are collectively referred to as vitamin D or calciferol.

The main natural source of vitamin D is endogenous production in the skin, upon exposure to sunlight. Ultraviolet B radiation in the wavelength range of 280 to 315 nm penetrates the skin and converts 7-dehydrocholesterol to a precursor of vitamin D3 (Allgrove, 2015; SACN, 2016). Few food sources naturally contain significant amounts of vitamin D. Vitamin D3 is found in oily fish, fish oils and egg yolk, whilst vitamin D2 can be obtained in small quantities from wild mushrooms (Misra et al, 2008; SACN, 2016). Certain food products are artificially fortified with vitamin D. In the United Kingdom (UK), infant formula milk and some margarines, cereals, and yoghurts are fortified. In the USA and Canada cow's milk is also fortified.

Both vitamin D3 and vitamin D2 follow a two-step metabolic pathway to generate the biologically active hormone 1,25-dihydroxyvitamin D, as summarised in Figure 2.1 (Allgrove, 2015; Basatemur et al, 2015; SACN, 2016). The first step involves hydroxylation in the liver to form 25-hydroxyvitamin D (25-OH-D). This is the major circulating form of vitamin D, and is the best available measure of an individual's vitamin D status (SACN, 2016). The second hydroxylation step is catalysed by the enzyme 1α-hydroxylase, to form 1,25-dihydroxyvitamin D. This is the main regulatory step in the vitamin D metabolic pathway. The principal site of 1α-hydroxylase activity is the kidney, however the enzyme is active in numerous other tissues where it is believed to have a paracrine role. The activity of 1α-hydroxylase is stimulated by parathyroid hormone (PTH), and inhibited by 1,25-dihydroxyvitamin D creating a negative feedback loop.

**Figure 2.1** Overview of vitamin D metabolism.[a]




[a] Figure adapted from Crawford et al (2006).

1,25-dihydroxyvitamin D acts via the vitamin D receptor, a member of the superfamily of nuclear receptors, to modify gene transcription. The main function of 1,25-dihydroxyvitamin D is to regulate calcium and phosphate metabolism and homeostasis, which in turn is essential for ensuring normal neuronal and muscular function and adequate bone mineralisation. The classical actions of 1,25-dihydroxyvitamin D are to

increase intestinal absorption of calcium and phosphate, decrease renal excretion of calcium, and stimulate osteoclast mediated calcium resorption from the skeleton and promote bone remodelling.

## 2.3 Clinical Consequences of Vitamin D Deficiency in Children

### *2.3.1 Pathophysiology*

In the early stages of vitamin D deficiency, impaired intestinal absorption of calcium causes hypocalcaemia (low serum calcium levels), which may or may not be symptomatic (Allgrove & Shaw, 2015; Shaw & Mughal, 2013a). The hypocalcaemia in turn stimulates parathyroid hormone (PTH) secretion, which acts to: i) reduce renal calcium excretion, ii) increase renal phosphate excretion, iii) stimulate renal 1α-hydroxylase activity resulting in increased 1,25-dihydroxyvitamin D production, and iv) stimulate calcium release from the bone by promoting osteoclast activity (Allgrove, 2015). This secondary hyperparathyroidism acts to normalise serum calcium levels, however the combination of hypophosphataemia (low serum phosphate levels) and increased osteoclast activity results in demineralisation of the bone. In growing children this results in rickets, a childhood metabolic bone disease caused by under-mineralisation of the growing bone before the epiphyses (growth plates) have closed. After the growth plates have fused, in older children and adults, the term osteomalacia is used to describe the demineralisation of bone at sites of bone remodelling.

In the later stages of vitamin D deficiency, 25-OH-D levels fall to the extent that there is insufficient substrate for 1,25-dihydroxyvitamin D synthesis. The PTH response is then no longer able to maintain normal serum calcium levels, and hypocalcaemia occurs. Hypocalcaemia lowers the threshold for nerve and muscle cell depolarisation, causing neuromuscular irritability. Vitamin D deficiency is also thought to adversely affect skeletal muscle function, although it is not clear whether this effect is a direct result of 1,25-dihydroxyvitamin D action on myocytes, or is an indirect effect of hypophosphataemia and hypocalcaemia (Reid, 2016).

### 2.3.2 Clinical Presentation

In children, vitamin D deficiency can present clinically with symptoms or signs related to the skeletal effects of rickets and osteomalacia, with symptoms arising from muscle weakness, or with sequelae of hypocalcaemia, as summarised in Table 2.1 (Dimitri & Bishop, 2007; Shaw & Mughal, 2013a). The classical long-bone deformities of rickets are typically seen in infants and toddlers once they are mobilising and weight bearing. Adolescents often present with vague symptoms of musculoskeletal aches and pains and muscle weakness. Hypocalcaemic symptoms tend to present either in young children in the first two years of life, or in adolescents.

**Table 2.1** Clinical features with which vitamin D deficiency can present in children.

| Clinical features | Additional notes |
|---|---|
| **Skeletal features** | |
| • Long bone deformities | Bowing deformities affect weight-bearing limbs, with forearm deformities occurring in crawling infants, and bow legs (genu varum) or knock knees (genu valgum) seen in walking children. |
| • Swelling of the joints and costochondral junctions | Caused by deposition of excessive cartilage, typically involving the wrist and ankle joints. Swelling of the costochondral junctions results in a 'string of beads' appearance on the anterior rib cage (termed rickety rosary). |
| • Cranial signs | Include frontal bossing of the skull, delayed fontanelle closure, and craniotabes (softening of the skull bones which are depressible upon pressure, seen in infants). |
| • Kyphoscoliosis | Pathological curvature of the spine. |
| • Poor growth | |
| • Musculoskeletal pain | Thought to be the cause of irritability seen in infants with rickets. Causes non-specific limb pains in older children. |
| • Pathological fractures | The under-mineralised bone may predispose to fractures. |
| • Dental features | Delayed tooth eruption and enamel hypoplasia (which increases the risk of dental caries). |
| **Muscle weakness** | |
| • Proximal myopathy | May present with difficulty in climbing stairs, or gait disturbance. |
| • Delayed motor milestones | For example, delay in walking. |
| **Hypocalcaemia** | |
| • Seizures | |
| • Tetany | Generalised involuntary muscle contractions, or localised to the hands and feet (carpopedal spasm). |
| • Cardiac complications | Include prolongation of the QT interval, arrhythmias, and cardiomyopathy that presents with cardiac failure and can be fatal. |
| • Stridor | Due to laryngospasm. |

There are various causes of rickets, vitamin D deficiency being the most common aetiology in regions of the world where the majority of countries have high-income economies (Europe, North America, Australasia). In low- and middle-income countries, particularly in Africa and Asia, dietary calcium deficiency is a common cause of rickets (Creo et al, 2017; Mughal, 2011; Prentice, 2013). Inadequate calcium intake has also been reported to be a contributing factor in cases of rickets reported from high-income countries such as the USA (DeLucia et al, 2003). Rickets can also be caused by rare genetic defects affecting the vitamin D metabolic pathway or phosphate metabolism (Dimitri & Bishop, 2007; Mughal, 2011).

The biochemical profile seen in children with vitamin D deficiency rickets includes a low 25-OH-D level, raised PTH, and raised alkaline phosphatase (ALP). Serum phosphate levels are normal or elevated in early stages of vitamin D deficiency, but subsequently become low when the secondary hyperparathyroid response is established (Allgrove & Shaw, 2015). Calcium levels can be low or normal depending on the stage of vitamin D deficiency (see section 2.3.1). The classical radiological signs of rickets are cupping, fraying, and widening of the metaphysis at the ends of the long bones. Other radiological features that may be seen include generalised osteopenia, and a periosteal reaction along the diaphysis (shaft) of the bone.

### *2.3.3 Treatment*

Symptomatic vitamin D deficiency is treated with either colecalciferol or ergocalciferol, which are most commonly given as a once daily oral dose over a treatment course of between 1 to 3 months. Doses of between 1,000 to 10,000 International Units (IU) per day are used depending on the age of the child, and various different dosing guidelines exist internationally (Misra et al, 2008; Munns et al, 2016; RCPCH, 2013). As an alternative strategy to daily dosing, vitamin D deficiency can be treated with a large dose of calciferol given as a single dose, or in divided doses over a short period of time. This is known as stoss therapy (from the German for “push”), and typically involves the administration of doses between 100,000 to 600,000 IU, either orally or by intramuscular injection (Misra et al, 2008; Munns et al, 2016). This approach can be particularly useful in situations of poor compliance with medication, however concerns exist regarding a risk of adverse effects, with case reports of markedly elevated 25-OH-D levels, hypercalcaemia, hypercalciuria, and nephrocalcinosis following large treatment doses in children (Vogiatzi et al, 2014).

Activated analogues of vitamin D, such as alfacalcidol (1α-hydroxycolecalciferol) and calcitriol (1,25-dihydroxyvitamin D), are not routinely recommended in the treatment of primary vitamin D deficiency (Allgrove & Shaw, 2015; Elder & Bishop, 2014). They are ineffective at replenishing vitamin D stores, and require closer monitoring as their use carries a risk of hypercalcaemia. However, they may be used in the acute phase when there is clinically significant hypocalcaemia secondary to vitamin D deficiency, until calcium levels have normalised (Arundel & Shaw, 2015; Munns et al, 2006). They are also indicated in situations where there is impaired vitamin D metabolism, such as renal impairment, liver disease, or genetic defects affecting the vitamin D or phosphate metabolic pathways, and in hypoparathyroidism (Allgrove & Shaw, 2015).

Children who are hypocalcaemic at presentation require calcium replacement in addition to vitamin D, and this may also be considered in children with normal serum calcium but a low dietary calcium intake (Shaw & Mughal, 2013a). Most children make a full recovery following appropriate treatment, however residual skeletal deformities may remain in some cases.

Evidence is limited regarding the management of asymptomatic children with an incidental finding of biochemical vitamin D deficiency (defined as a 25-OH-D level <25 nmol/l in the UK, see section 2.4 below). Some sources recommend a course of treatment dose vitamin D as described above for symptomatic deficiency (Arundel & Shaw, 2015; Misra et al, 2008), whilst others advise low-dose maintenance supplements (400 to 800 IU per day) and lifestyle advice regarding safe sun exposure (Shaw & Mughal, 2013b).

### *2.3.4 Bone Mass Accrual*

Peak bone mass is attained in early adulthood, with 90% of adult bone mineral content achieved by the end of adolescence, and the greatest increase in bone mass occurring between 12 to 17 years of age (Lewis & Laing, 2015; Winzenberg & Jones, 2013). Peak bone mass is considered to be an important determinant of the risk of osteoporotic fractures in later life (Shaw & Mughal, 2013a). It has been suggested that vitamin D deficiency may impair bone mass accrual during childhood, and adversely affect peak bone mass. However, evidence from randomised controlled trials is inconsistent (Lewis & Laing, 2015). A systematic review of placebo-controlled randomised controlled trials found no overall effect of vitamin D supplementation on bone mineral content in children (Winzenberg et al, 2011). However, in planned

subgroup analysis limited to individuals with low baseline 25-OH-D levels (defined as <35 nmol/l), vitamin D supplementation was associated with higher total body bone mineral content. The authors suggested that it is unlikely that vitamin D supplementation is beneficial in increasing bone density in vitamin D replete children, however in those with suboptimal vitamin D status supplementation may have clinically useful benefits for skeletal health.

## 2.4 Definition of Vitamin D Deficiency

Vitamin D status is defined on the basis of serum 25-hydroxyvitamin D (25-OH-D) levels, as this is the major circulating form of vitamin D and reflects both endogenous synthesis and dietary intake. However, the extent to which 25-OH-D levels reflect how well the physiological requirements of the body for vitamin D are being met is unclear, and 25-OH-D levels do not correlate well with health outcomes such as rickets (SACN, 2016). As a result of this uncertainty, the choice of 25-OH-D thresholds considered to represent deficiency and sufficiency are controversial and vary internationally across different guidelines and reports.

In the UK, the British Paediatric and Adolescent Bone Group, the Royal College of Paediatrics and Child Health (RCPCH), and the National Osteoporosis Society all recommend the following thresholds for the interpretation of serum 25-OH-D levels in children (Arundel et al, 2012; Arundel & Shaw, 2015; RCPCH, 2013):

| | |
|---|---|
| 25-OH-D <25 nmol/l: | Deficiency |
| 25-OH-D 25-50 nmol/l: | Insufficiency / may be inadequate in some people |
| 25-OH-D >50 nmol/l: | Sufficiency |

The UK Scientific Advisory Committee on Nutrition (SACN) considers the 25-OH-D threshold of 25 nmol/l as the level below which the risk of poor musculoskeletal health is increased (SACN, 2016). This threshold for vitamin D deficiency is based on the observation that 25-OH-D levels are <25 nmol/l in the majority of reported cases of symptomatic vitamin D deficiency in children (e.g. rickets or hypocalcaemia). However, several case series have reported symptomatic vitamin D deficiency in children with higher 25-OH-D levels between 25 to 50 nmol/l (Ahmed et al, 2011; Sharma et al, 2009; Wheeler et al, 2015). Furthermore, the 25-OH-D cut-off of <25 nmol/l is not a clinical threshold diagnostic of disease, as the majority of children with 25-OH-D levels

<25 nmol/l are asymptomatic and do not exhibit any clinical or biochemical features of rickets. The British Paediatric and Adolescent Bone Group acknowledges that the evidence base underpinning the choice of 25-OH-D thresholds in children and adolescents is limited (Arundel et al, 2012). Internationally, definitions of vitamin D deficiency vary across different guidelines, as summarised in Table 2.2. The interpretation of serum 25-OH-D levels is further complicated by the variability in results obtained using different laboratory assay methods (Lai et al, 2010; SACN, 2016).

**Table 2.2** Definitions of vitamin D status used in international guidelines.

| Guidelines | 25-OH-D Thresholds | |
|---|---|---|
| - US Institute of Medicine (IOM, 2011)<br>- International paediatric consensus recommendations (Munns et al, 2016)<br>- French Society of Paediatrics (Vidailhet et al, 2012) | <30 nmol/l:<br>30-50 nmol/l:<br>>50 nmol/l: | severe deficiency<br>moderate deficiency<br>sufficiency |
| - European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Braegger et al, 2013) | <25 nmol/l:<br>>50 nmol/l: | severe deficiency<br>sufficiency |
| - American Academy of Pediatrics (Wagner & Greer, 2008) | <50 nmol/l:<br>>50 nmol/l: | deficiency<br>sufficiency |
| - Australia and New Zealand paediatric consensus recommendations (Munns et al, 2006) | <12.5 nmol/l:<br>12.5-25 nmol/l:<br>25-50 nmol/l:<br>>50 nmol/l: | severe deficiency<br>moderate deficiency<br>mild deficiency<br>sufficiency |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D

## 2.5 Determinants of Vitamin D Status

The main natural source of vitamin D is endogenous production in the skin upon exposure to sunlight, as there are few natural food sources. Exposure to sunlight is therefore an important determinant of 25-OH-D status. At latitudes above approximately 40° from the equator, ultraviolet B radiation of the appropriate wavelength required to facilitate cutaneous vitamin D synthesis is only present at limited times during the middle of the day, during certain months of the year (Prentice, 2008). In the UK (which is at a latitude of 50–60° North), exposure to ultraviolet radiation effective for vitamin D synthesis is minimal during the winter months, and

seasonal differences in population 25-OH-D levels have been observed (SACN, 2016). Lifestyle factors and disabilities can limit outdoor activity, and restrict sunlight exposure. Excessive sunscreen use can also impair cutaneous vitamin D synthesis.

Ethnicity is an important determinant of vitamin D status (Mithal et al, 2009). The skin pigment melanin absorbs ultraviolet radiation. Therefore, individuals with darker coloured skin (brown or black) produce less vitamin D that people with lighter skin tones, when exposed to a constant dose of ultraviolet B radiation (Prentice, 2008; SACN, 2016). Cultural or religious clothing practices involving covering of most of the skin surface area limit sunlight exposure. Examples include traditional clothing worn by girls and women from some Muslim communities, such as the hijab (covering the body and head) and niqab (also covering the face). Furthermore, in certain cultures, for example some South and East Asian communities, people avoid sunlight exposure because fair skin is considered to be associated with beauty (Chen et al, 2017).

Although there are few natural dietary sources of vitamin D, the regular consumption of food products artificially fortified with vitamin D, fish liver oils, or vitamin D supplements can have a substantial influence on vitamin D status. Setting recommendations for dietary reference values for vitamin D is complicated by the ability of humans to synthesise vitamin D endogenously through exposure to sunlight. However, the UK Scientific Advisory Committee on Nutrition has set a reference nutrient intake (RNI) for vitamin D of 400 IU (10 micrograms) per day for all people in the general population aged 4 years and above (SACN, 2016). The RNI was derived by estimating the average intake that is required for the majority (97.5%) of the population to maintain serum 25-OH-D levels ≥25 nmol/l. There was insufficient data available to derive an RNI for children under 4 years of age, however SACN recommended a 'safe intake' of between 340 to 400 IU (8.5 to 10 micrograms) per day for infants under 1 year of age, and 400 IU per day for children aged from 1 year up to 4 years. It was not possible for SACN to quantify and take account of sunlight exposure when setting the dietary reference values, because of the wide range of factors that affect endogenous vitamin D synthesis. Hence, the RNI was calculated under the assumption of minimal exposure to ultraviolet B radiation through sunlight (as is the case in winter months in the UK). The dietary reference values refer to intake from all dietary sources: natural food sources, fortified foods (including infant formula milk), and supplements. Based on data from the National Diet and Nutrition Survey conducted between 2008 to 2012, mean dietary intakes of vitamin D (including from supplements) among children in the UK were between only 24% to 27% of the RNI / 'safe intake' values recommended by SACN (Bates et al, 2014).

Various medical conditions can interfere with vitamin D absorption or metabolism. In renal disease, reduced activity of 1α-hydroxylase can impair the conversion of 25-OH-D to its active metabolite 1,25-dihydroxyvitamin D. In liver disease, the hydroxylation of calciferol to 25-OH-D may be impaired, and conditions associated with cholestasis (impaired bile flow from the liver into the intestine) can interfere with the gastrointestinal absorption of vitamin D. Other conditions associated with gastrointestinal malabsorption can also predispose to vitamin D deficiency, for example cystic fibrosis, coeliac disease, and inflammatory bowel disease. Obesity is associated with lower 25-OH-D levels, and it has been suggested that excessive adipose tissue may act as a sink for vitamin D, reducing its bioavailability (Prentice, 2008). Polymorphisms in genes involved in the vitamin D metabolic pathway are also likely to influence 25-OH-D status (Dastani et al, 2013).

The vitamin D status of newborns is directly dependent upon the vitamin D status of their mothers during pregnancy. 25-OH-D readily crosses the placenta, and 25-OH-D levels in umbilical cord blood (which represents vitamin D status in the newborn) have been shown to be between 80% to 100% of maternal 25-OH-D levels (Thandrayen & Pettifor, 2012).

## 2.6 Historical Context in the UK

Prior to 1900 rickets was widespread throughout urban parts of the UK, due to atmospheric pollution from coal fires, overcrowded housing conditions, and poor diets related to poverty (Hardy, 2003). In the late 19$^{th}$ and early 20$^{th}$ centuries the beneficial effects of sunlight exposure and cod liver oil ingestion on the prevention and treatment of rickets were identified (Elder & Bishop, 2014). The incidence of rickets declined dramatically from the 1920's onwards due to improved living conditions, a reduction in atmospheric pollution, distribution of cod liver oil to pregnant women and young children, and the practice of outdoor 'airing' of infants (Bivins, 2007).
During the Second World War, mandatory fortification of certain food products with vitamin D was introduced, including dried milk, infant cereals, and margarine. However, reports of cases of infantile hypercalcaemia in the 1950's, attributed to excessive fortification of baby milks and food with vitamin D, resulted in food fortification policy being reversed (Bivins, 2007; Stewart et al, 1964). From the 1960's reports were published of rickets returning among South Asian immigrant communities (Bivins, 2007; Ford et al, 1972; Ford et al, 1976), and local public health campaigns were

developed to prevent rickets through the distribution of vitamin D supplements to high-risk groups (Dunnigan et al, 1981). In the 1990's the teratogenicity of excessive vitamin A intake was recognized, and cod-liver oil was no longer recommended or provided to pregnant women, without provision being made for alternative vitamin D supplementation in pregnancy (Hyppönen & Boucher, 2010).

## 2.7 Contemporary Epidemiology of Childhood Vitamin D Deficiency in the UK

When considering the epidemiology of vitamin D deficiency, biochemical deficiency (defined on the basis of serum 25-OH-D levels) needs to be distinguished from symptomatic complications of vitamin D deficiency. The majority of children with low 25-OH-D levels are asymptomatic and do not exhibit any clinical or biochemical features of rickets or hypocalcaemia.

### *2.7.1 Biochemical Vitamin D Status*

A number of cross-sectional studies have investigated biochemical vitamin D status, determined using serum 25-OH-D levels, in healthy children in the UK (Table 2.3). Using the 25-OH-D thresholds recommended by the British Paediatric and Adolescent Bone Group and the RCPCH (see section 2.4), it is clear that a substantial proportion of the paediatric population have vitamin D levels that are considered to be suboptimal. The prevalence of vitamin D deficiency (25-OH-D <25 nmol/l) reported by the studies varied widely between 1.6% to 34%, depending on the ethnicity and age of participants, and the prevalence of vitamin D insufficiency (25-OH-D 25-50 nmol/l) varied between 29% to 85%.

25-OH-D levels exhibit a strong seasonal variation in UK children, with higher levels seen in summer and autumn months compared to winter and spring (Absoud et al, 2011; Farrar et al, 2016; Tolppanen et al, 2012). Vitamin D levels are considerably lower in children from non-white compared to white ethnic backgrounds (Absoud et al, 2011; Tolppanen et al, 2012).

**Table 2.3** Studies investigating biochemical vitamin D status in UK children.

| Study | Study date | Sample size | Participant characteristics | % of children with 25-OH-D below specified levels |
|---|---|---|---|---|
| Bates et al (2014) | 2008 to 2012 | 802 | Age: 1.5 to 18 years<br>Ethnicity not reported | 25-OH-D <25 nmol/l:<br>- age 1.5 to 3 years: 7.5%<br>- age 4 to 10 years: 14%<br>- age 11 to 18 years: 22% |
| Das et al (2006) | 2003 | 51 | Age: 14 to 16 years<br>Ethnicity:<br>- 27% white<br>- 73% non-white<br>All female | 25-OH-D <12.5 nmol/l: 17%<br>25-OH-D <30 nmol/l: 73% |
| Tolppanen et al (2012) | 1998 to 2005 | 7,560 | Age: 7 to 13 years<br>Ethnicity:<br>- 95% white<br>- 5% non-white | 25-OH-D <25 nmol/l: 1.6%<br>25-OH-D <50 nmol/l: 29% |
| Absoud et al (2011) | 1997 to 1998 | 1,102 | Age: 4 to 18 years<br>Ethnicity:<br>- 91% white<br>- 9% non-white | 25-OH-D <50 nmol/l:<br>- white: 30%<br>- non-white: 85% |
| Lawson & Thomas (1999) | 1996 | 618 | Age: 1.5 to 2.5 years<br>Ethnicity:<br>- 45% Indian<br>- 32% Pakistani<br>- 22% Bangladeshi | 25-OH-D <25 nmol/l:<br>- Indian: 25%<br>- Pakistani: 34%<br>- Bangladeshi: 20%<br>25-OH-D <50 nmol/l:<br>- Indian: 70%<br>- Pakistani: 81%<br>- Bangladeshi: 69% |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D

### *2.7.2 Symptomatic Vitamin D Deficiency*

Over the last two decades, anecdotal observations have raised concerns that the number of children presenting to healthcare services in the UK with symptomatic vitamin D deficiency has been increasing (Allgrove, 2004; Davies & Shaw, 2011; Shaw & Pal, 2002). However, there is limited data available regarding the epidemiology of symptomatic vitamin D deficiency among children in the UK. Most of the existing studies have been retrospective single- or multi-centre case series, without denominator data available for the calculation of incidence (Table 2.4).

**Table 2.4** Studies investigating symptomatic vitamin D deficiency in UK children.

| Study | Study design | Time period | Setting | Summary of main results |
|---|---|---|---|---|
| El-Fakhri et al (2013) | Prospective surveillance study | Sept 2009 to August 2011 | Scotland | 109 children age 0-16 years with symptomatic VDD reported by paediatricians. 38% presented with bowed legs, 25% with bone pain. |
| Ahmed et al (2011) | Retrospective case series | 2002 to 2008 | Royal Hospital for Sick Children, Glasgow | 160 children aged 0-14 years identified with symptomatic VDD. 40% presented with bowed legs, 12% with seizures. |
| Sharma et al (2009) | Retrospective case series | Jan 2006 to June 2008 | 4 London hospitals | 74 infants (age <1 year) identified with symptomatic VDD. 27% presented with hypocalcaemic seizures. |
| Maiya et al (2008) | Retrospective case series | 2000 to 2006 | 4 paediatric cardiology centres in South East England | 16 infants identified with hypocalcaemia and dilated cardiomyopathy secondary to VDD. 3 died. |
| Callaghan et al (2006) | Prospective surveillance study | May 2000 to April 2001 | West Midlands | 24 children aged 0-4 years with symptomatic VDD reported by paediatricians. 46% presented with bowed legs, 25% with seizures, 17% with gross motor delay. Overall annual incidence of 7.5 per 100,000 children. |
| Ladhani et al (2004) | Retrospective case series | 1996 to 2001 | 4 London hospitals | 65 children aged 0-16 years identified with symptomatic VDD. 55% presented with musculoskeletal signs, 45% with symptoms of hypocalcaemia. |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; VDD, vitamin D deficiency.

The only study to report a reliable incidence estimate is a regional prospective surveillance study conducted in the West Midlands, which involved active case reporting by paediatricians (Callaghan et al, 2006). 24 cases of symptomatic vitamin D deficiency were identified between May 2000 and April 2001 in children aged 0 to 4 years, equating to an annual incidence of 7.5 per 100,000 children (confidence interval not reported). However, regional differences in ethnic demography limit the generalisability of the findings, as the West Midlands has a higher South Asian population than the national average: 12.3% compared to 6.7% nationally in England and Wales, among children aged 0 to 4 years in the 2001 Census (ONS, 2001). National data is lacking regarding the health burden caused by symptomatic vitamin D deficiency among children in the UK.

In all of the studies reporting symptomatic vitamin D deficiency among UK children (Table 2.4), the vast majority of cases (>90%) were from either South Asian, African-Caribbean, or Middle Eastern ethnic minority backgrounds.

## 2.8 UK Public Health Policy Regarding the Prevention of Vitamin D Deficiency

UK public health policy regarding the prevention of vitamin D deficiency is based upon the recommendation of vitamin D supplementation for high-risk population groups, including young children and pregnant women. Department of Health (DoH) guidance regarding vitamin D supplementation changed recently, following the publication of updated recommendations for vitamin D intake issued by the Scientific Advisory Committee on Nutrition (SACN, 2016). The population groups for whom vitamin D supplementation is recommended, in previous and current DoH guidance, are summarised in Table 2.5 (DoH, 2009; 2016). Following the updated SACN guidance, vitamin D supplements are now recommended from birth rather than 6 months for breastfed infants.

However, evidence suggests that the implementation of these recommendations has not been effective. In most regions of the country supplements for children and pregnant women are only provided free of charge to low-income families who qualify for the Healthy Start scheme. Healthy Start is a UK-wide, means tested, statutory scheme which provides food vouchers (that can be used to obtain milk, fruit and vegetables, and infant formula milk) and coupons for multivitamin supplements to pregnant women and mothers who are in receipt of income-related state benefits or child tax credits (with an annual family income of £16,190 or less) (McGee & Shaw, 2013). Pregnant women under the age of 18 are also eligible for the scheme, regardless of whether or not they receive benefits (Filby et al, 2015). The Healthy Start vitamin tablets for pregnant and lactating women contain vitamin D (400 IU), vitamin C, and folic acid. The Healthy Start vitamin drops for children contain vitamin D (300 IU in the recommended daily dose of 5 drops), vitamin A, and vitamin C. In a limited number of areas, local programmes have been introduced with universal provision of Healthy Start vitamins for all pregnant women and children (Moy et al, 2012).

**Table 2.5** Population groups for whom vitamin D supplementation is recommended, in previous and current DoH guidance.

| DoH guidance between 2007 and 2016 | Current DoH guidance |
|---|---|
| • Children aged from 6 months to 5 years who drink less than 500ml of formula milk per day. Supplements were recommended from 1 month of age for breastfed infants if there was doubt about the mother's use of vitamin supplements during pregnancy or breastfeeding. Recommended supplement of 280 to 340 IU per day. | • Infants from birth to 1 year of age, unless they are taking ≥500ml of formula milk per day. Recommended supplement of 340 to 400 IU per day.<br>• Children aged between 1 to 4 years. Recommended supplement of 400 IU per day. |
| • Pregnant and breastfeeding women. Recommended supplement of 400 IU per day. | • Pregnant and breastfeeding women. Recommended supplement of 400 IU per day. |
| • People aged ≥65 years. Recommended supplement of 400 IU per day. | • All people aged 5 years or older advised to consider taking a supplement of 400 IU per day during the autumn and winter. People from minority ethnic groups with dark skin advised to consider taking a supplement of 400 IU per day throughout the year. |
| • People with limited sunlight exposure. Recommended supplement of 400 IU per day. | • People with limited sunlight exposure. Recommended supplement of 400 IU per day. |

Abbreviations: DoH, Department of Health; IU, International Units
References: DoH (2009; 2016)

Uptake rates for Healthy Start vitamins among eligible families have been reported to be very low (<10%) across the country (Jessiman et al, 2013; Moonan et al, 2012). The overall use of vitamin supplements, whether Healthy Start or other brands, by young children in the general population is also low. In the national Infant Feeding Survey conducted between 2010 to 2011, 9% of breastfed infants were receiving vitamin drops at the age of six weeks, and 11% at four to six months of age (McAndrew et al, 2012). 14% of all children aged eight to ten months were receiving vitamin drops. In the National Diet and Nutrition Survey conducted between 2008 to 2012, the proportion of children reported to have used multivitamin supplements or cod liver oil at any point in the preceding year was 16% at age 1.5 to 3 years, 22% at age 4 to 10 years, and 18% at age 11 to 18 years (Bates et al, 2014).

Knowledge regarding the DoH recommendations for vitamin D supplementation among various groups of health professionals involved in the care of pregnant women and young children, as well as among parents, has been shown to be limited (Cleghorn, 2006; Jain et al, 2011; Sharma et al, 2011; Zipitis et al, 2011). Reasons that have been suggested for the poor uptake of Healthy Start vitamins include poor accessibility with limited distribution points for the vitamins, a lack of awareness among eligible families, and poor promotion of the scheme by healthcare professionals (Jessiman et al, 2013).

An alternative approach to supplementation for improving the vitamin D status of the population is the fortification of food products. Fortification of infant formula milk with vitamin D is mandatory across Europe and North America (SACN, 2016). In Canada, the fortification of milk and margarine with vitamin D is mandatory, whilst in the US almost all milk and most cereals are fortified on a voluntary basis. In the UK, most margarines and fat spreads, and some cereals, but not milk, are fortified on a voluntary basis. Although food fortification has been shown to be effective in increasing dietary vitamin D intake and population vitamin D levels in randomised controlled trials (Black et al, 2012), historical reports of toxicity arising from over-fortification highlight the need for careful regulation and monitoring of such approaches (Blank et al, 1995).

## 2.9 Recent Academic and Clinical Interest in Vitamin D

### *2.9.1 Proposed Extra-Skeletal Roles of Vitamin D*

Over the last two decades, there has been extensive research and interest regarding the possibility that vitamin D may have clinically relevant physiological activity beyond its established role in calcium and bone metabolism, and that vitamin D deficiency may have a role in the development of numerous extra-skeletal diseases. This has also generated considerable interest and coverage in the general media (Sattar et al, 2012).

The vitamin D receptor is expressed in many tissue and cell types, beyond those that mediate the classical actions of 1,25-dihydroxyvitamin D in calcium and bone metabolism (the kidney, intestine, and bone) (Rosen et al, 2012). *In vitro* studies have demonstrated that 1,25-dihydroxyvitamin D can influence cell differentiation and cell proliferation, and modulate immune responses under experimental conditions (Rosen et al, 2012). Numerous observational studies, the majority of which involve adult populations, have suggested associations between lower 25-OH-D levels and

increased risk of a wide range of medical conditions including various cancers, cardiovascular disease, asthma and other atopic disorders, autoimmune conditions such as multiple sclerosis and diabetes mellitus, and infectious diseases such as Tuberculosis and acute respiratory tract infections (SACN, 2016; Theodoratou et al, 2014). However, for many of the health outcomes investigated, studies are conflicting and associations are inconsistent. Systematic reviews of randomised controlled trials (RCTs), largely involving elderly participants, have suggested that vitamin D supplementation may reduce overall mortality risk (Bjelakovic et al, 2014; Chowdhury et al, 2014). A recent meta-analysis of individual participant data from RCTs suggested a small protective effect of vitamin D supplementation against the risk of developing acute respiratory tract infections (Martineau et al, 2017). However, for most of the conditions reported to be associated with 25-OH-D levels in observational studies, adequately powered RCTs investigating the effect of vitamin D supplementation on disease prevention or treatment are either lacking or provide null results (SACN, 2016; Theodoratou et al, 2014).

Fewer RCTs have been conducted investigating the effect of vitamin D on non-skeletal outcomes in children. High-dose colecalciferol given every 3 months did not reduce the risk of lower respiratory tract infections or diarrhoeal illness in infants recruited to a large placebo-controlled RCT in Afghanistan (Aluisio et al, 2013; Manaseki-Holland et al, 2012). A weekly dose of 1,400 IU of colecalciferol did not reduce hospital admissions, clinic attendance, or mortality during the first 6 months of life among low-birthweight (<2.5 kg) infants recruited to a large placebo-controlled RCT in India (Kumar et al, 2011). A systematic review identified few trials investigating the effect of vitamin D supplementation on asthma control in children, with inconclusive results (Fares et al, 2015).

There are various possible explanations why the associations seen in observational studies may be misleading (Harvey & Cooper, 2012; Reid, 2016). Observed associations may be due to reverse causation; illness may cause reduced physical activity and exposure to sunlight, and it has also been proposed that systemic inflammation may itself reduce 25-OH-D levels (Reid et al, 2011; Waldron et al, 2013). Associations may be confounded by factors such as body mass index, and publication bias may distort the balance of the literature in favour of positive findings. The UK Scientific Advisory Committee on Nutrition and the US Institute of Medicine have concluded that, at present, convincing evidence does not exist for a beneficial effect of vitamin D on non-musculoskeletal health outcomes (IOM, 2011; SACN, 2016).

### 2.9.2 Vitamin D Testing and Treatment in Clinical Practice

In addition to the growth in academic research and media interest in vitamin D, there is also evidence that vitamin D has attracted increasing attention in clinical practice over the last decade. In England, overall NHS expenditure on vitamin D prescriptions dispensed by community pharmacies has more than tripled from £28 million in 2004 to £92 million in 2014 (HSCIC, 2005; 2015b). Individual hospital biochemistry departments in the UK have reported large increases in requests for vitamin D tests; a 10-fold increase was seen at the Homerton Hospital in East London between 2006 to 2010 (Kotta et al, 2015), and a 2-fold increase at the Glasgow Royal Infirmary between 2008 to 2010 (Sattar et al, 2012). In Australia, national rates of 25-OH-D testing increased over 50-fold from 59 tests per 100,000 people in 2001 to 3,648 tests per 100,000 people in 2011, whilst in the Ontario province of Canada there was a 25-fold increase in testing between 2004 to 2010, with large associated increases in healthcare expenditure (Bilinski & Boyages, 2012; 2013). Although large increases in vitamin D testing and treatment have been reported in adult practice, trends in the diagnosis of vitamin D deficiency have not been specifically investigated in children, either in the UK or internationally.

## Chapter 3

# The Global Incidence of Symptomatic Vitamin D Deficiency in Children: A Systematic Review

## 3.1 Introduction

Over the last two decades, reports have raised concerns that clinical complications of vitamin D deficiency, such as rickets and hypocalcaemia, have increased in frequency among children in developed countries (Allgrove, 2004; Davies & Shaw, 2011; Holick, 2006; Robinson et al, 2006; Shaw & Pal, 2002). However, the majority of studies investigating symptomatic vitamin D deficiency in children are limited to single and multi-centre case series, which are not derived from defined populations, and therefore lack the denominator data required to calculate incidence or prevalence estimates. Systematic reviews have been undertaken to investigate biochemical vitamin D status, assessed using serum 25-hydroxyvitamin D (25-OH-D) levels, in populations worldwide (Hilger et al, 2014; Saraf et al, 2016). However, the epidemiology of symptomatic vitamin D deficiency in children has not been systematically reviewed. This chapter describes a systematic literature review and meta-analysis undertaken to explore the incidence of symptomatic vitamin D deficiency in children worldwide, and investigate differences in incidence by demographic factors.

## 3.2 Aims and Objectives

### *3.2.1 Review Aims*

The overall aim was to systematically review studies which report the contemporary incidence of symptomatic vitamin D deficiency among children worldwide.

### *3.2.2 Review Objectives*

i) To investigate the incidence of symptomatic vitamin D deficiency in children worldwide, between 1990 to 2016.

ii) To investigate differences in the incidence of symptomatic vitamin D deficiency in children by ethnicity, age, and sex.

iii) To investigate temporal trends in the incidence of symptomatic vitamin D deficiency in children, between 1990 to 2016.

## 3.3 Methods

### *3.3.1 Research Question*

The primary research question for the systematic review, which was used as the basis upon which to develop the search strategy, was: *What is the contemporary incidence of symptomatic vitamin D deficiency in children worldwide?* Symptomatic vitamin D deficiency was defined as one or more of the recognised clinical complications or symptoms that can be caused by vitamin D deficiency in children, including rickets and hypocalcaemia (see chapter 2.3.2).

### *3.3.2 Measures of Disease Frequency*

The most commonly used measures of disease frequency fall into two broad categories: prevalence and incidence (Hennekens & Buring, 1987). Prevalence quantifies the proportion of people within a population who have a certain disease (existing cases) at a given point, or during a specified period, in time. In contrast, measures of incidence describe how often new cases of a disease occur within a population during a given period of time.

There are two main types of incidence measures: incidence risk and incidence rate. Incidence risk quantifies the proportion of individuals at risk of developing a disease who develop the disease during a certain time period. The denominator in the calculation is the number of people at risk of developing the disease at the start of the time period (the total population at risk):

$$Incidence\ risk\ = \frac{Number\ of\ new\ cases\ of\ a\ disease\ during\ a\ given\ time\ period}{Population\ at\ risk\ at\ the\ start\ of\ the\ time\ period}$$

Incidence risk is also referred to in the literature as cumulative incidence or incidence proportion. In the calculation of incidence risk an assumption is made that the entire population at risk is followed-up, and remains at risk, throughout the whole of the study time period. In contrast, incidence rate quantifies the frequency of occurrence of new cases of a disease in a population in relation to the total person-time at risk during the study time period, allowing for varying time-periods of follow-up between individuals:

$$Incidence\ rate\ = \frac{Number\ of\ new\ cases\ of\ a\ disease\ during\ a\ given\ time\ period}{Total\ person\text{–}time\ at\ risk\ during\ the\ period}$$

As the research objective for this review was concerned with exploring the frequency of occurrence of symptomatic vitamin D deficiency in populations of children worldwide, it was limited to studies reporting estimates of incidence. Studies reporting prevalence were not included, as prevalence is influenced not only by the risk of developing a condition but also by factors which determine the duration of illness, such as access to healthcare.

### *3.3.3 Study Inclusion and Exclusion Criteria*

Studies were considered eligible for inclusion if they met all of the following inclusion criteria:

i) The study reported symptomatic vitamin D deficiency as an outcome (defined as one or more of the recognised clinical complications or symptoms that can be caused by vitamin D deficiency in children, including rickets and hypocalcaemia).

ii) An estimate for incidence rate or incidence risk (also known as cumulative incidence or incidence proportion) was given, or sufficient information was provided from which to calculate an incidence estimate.

iii) The data was drawn from a general population of children, or a sample of the general population, in a defined geographical area.

iv) The study reported original research.

Studies were excluded if they met any of the following exclusion criteria:

i) The outcome reported was biochemical vitamin D deficiency identified through the screening of asymptomatic individuals, or the distribution of vitamin D levels in a population, as opposed to symptomatic vitamin D deficiency.

ii) The data was not drawn from a general population of children, for example where the study population was limited to children with a co-morbidity (for example renal disease) or to children receiving healthcare services (for example patients in intensive care units, or attending outpatient clinics).

iii) The study did not include children (age <18 years), or if the study population included both adults and children the data provided did not allow incidence estimates to be calculated separately for children.

iv) The study reported data covering a time period prior to 1990. The intention was to investigate contemporary data, considered to be informative regarding the current epidemiology of symptomatic vitamin D deficiency in children.

v) Duplicate reports of the same data. Where multiple publications presented identical or overlapping data, the most comprehensive and informative version of the study was included and the other related papers were excluded.

vi) The study full-text was not obtainable through the University College London libraries, the British Library, the M25 Consortium of Academic Libraries (http://www.m25lib.ac.uk), online, or following e-mail request sent to the corresponding author.

There was no specific restriction by study type or design, other than that the study methodology had to allow the derivation of an incidence estimate. In the case of interventional studies, only incidence estimates from a control or no-intervention study arm were included. There was no restriction by geographical location or language.

### *3.3.4 Search Strategy*

The following bibliographic databases were searched to identify relevant published literature: MEDLINE, EMBASE, PsycINFO, CINAHL, Web of Science, and Global Health. An initial search was carried out on 30th October 2014, and included studies published from 1st January 1990 onwards. An updated search was carried out on 2nd April 2017, and included studies published between 1st January 2014 and 31st December 2016. The reference lists of studies that met the inclusion criteria, and of relevant review articles (identified by the search or already known to the author), were also hand-searched to identify additional relevant work. A summary of the search terms used as the basis for the search strategy across databases was as follows:

Concept 1: 'vitamin d deficiency', rickets, osteomalacia, 'hypovitaminosis D', OR 'avitaminosis D'

AND

Concept 2: incidence, prevalence, OR epidemiolog* [1]

AND

Concept 3: child*, infant*, infancy, neonat*, newborn*, baby, babies, toddler*, adolescen*, teenage*, 'young person*', 'young people*', youth, paediatric*, pediatric*, kid*, OR juvenile*

The search term for prevalence was included so that papers reporting a prevalence estimate could be reviewed, to ensure that the epidemiological terminology was correctly used and that the study did not in fact contain an estimate of incidence. The detailed search terms used for each of the bibliographic databases are described in appendix C. Search strategies were designed such that searches of database subject headings as well as free-text searches were included for each search term of interest.

### *3.3.5 Study Selection and Data Extraction*

The search results from each of the databases were imported into the EndNote X7 software package (Clarivate Analytics), and duplicate records were identified and removed. The titles and abstracts of all remaining references were screened, and any articles that were clearly not relevant to the study question or did not meet the study inclusion criteria were excluded at this stage. For articles written in a language other than English, Google Translate (https://translate.google.co.uk) was used to translate the text to English. The full text was obtained for all articles that were deemed to be potentially relevant at the title and abstract review stage, and the full text was analysed to determine study eligibility based on the pre-determined criteria (see section 3.3.3). For each study deemed eligible for inclusion, a standardised data collection form was used to extract information regarding study characteristics, methodology, participant characteristics, relevant outcomes, and indicators of the quality of study reporting and design (see Tables 3.1 & 3.3).

[1] The symbol * represents truncation of a search term, to identify all words starting with a particular combination of letters. For example, the search term epidemiolog* will find references containing the words epidemiology and epidemiological.

### 3.3.6 Critical Appraisal of Included Studies

Studies included in the systematic review were critically appraised to assess their methodological quality, the quality of study reporting, and the risk of bias influencing the incidence estimates. Whilst a number of guidelines for the critical evaluation of prevalence studies have been published (Boyle, 1998; Hoy et al, 2012; Loney et al, 1998), no quality-assessment tools have been developed specifically for studies reporting disease incidence. Therefore, the criteria used to assess study quality and risk of bias were developed ad hoc specifically for this study.

A list of quality indicators for study reporting and methodology, considered to be relevant for the assessment of studies investigating the incidence of symptomatic vitamin D deficiency, was compiled (Table 3.1). This list was developed with reference to existing guidelines for the reporting of observational epidemiological studies (Vandenbroucke et al, 2007), published guidelines for the appraisal of prevalence studies (Boyle, 1998; Hoy et al, 2012; Loney et al, 1998), and previously published systematic reviews of disease incidence (Ferris et al, 2017; Tibazarwa et al, 2008). As there are no validated diagnostic criteria available for clinical complications of vitamin D deficiency, such as rickets, the use of accepted diagnostic criteria could not be included as a study quality indicator.

The risk of bias in study results (i.e. the internal validity of included studies) was assessed by considering three sources of systematic error that were considered to be of particular relevance to studies of disease incidence; the risk of case misclassification, the risk of case under-ascertainment, and inaccuracy in the estimation of the population at risk (denominator). The risk of systematic error arising from each of these sources was graded as low, moderate, or high, using criteria developed specifically for this study described in Table 3.2. The external validity of included studies was also assessed by considering the generalisability of the study results to the national population (see Table 3.2).

A subgroup of studies considered to be of higher overall methodological quality included those in which: i) the risk of case misclassification was moderate or low, ii) the risk of case-under-ascertainment was moderate or low, iii) the reliability of the population at risk estimate was moderate or high, and iv) the generalisability to the national population was moderate or high.

**Table 3.1** Quality indicators for study reporting and methodology.

| Quality indicator | Additional notes |
|---|---|
| • Is the study population clearly defined? | |
| • Does the study population represent either an entire population survey, or a random sample taken from the general population? | Not true if the study population represents a convenience based sample of the general population (e.g. individuals registered with a particular healthcare provider). |
| • Are the study inclusion and exclusion criteria clearly specified? | |
| • Is the study time period clearly specified? | |
| • Is the case definition clearly specified? | |
| • Does the case definition include an assessment of vitamin D status? | Considered important to reduce the risk of case misclassification, as clinical complications such as rickets can have causes other than vitamin D deficiency (e.g. dietary calcium deficiency). |
| • Did case ascertainment or validation involve clinical assessment or review of medical notes? | Not true for studies where case status was defined entirely on the basis of diagnostic codes in healthcare / administrative databases. |
| • Response rate | Only applicable for studies involving primary data collection (as opposed to secondary analysis of existing datasets). |
| • Were multiple sources used for case ascertainment? | In the case of surveillance studies, was there more than one source of case reporting? In the case of database studies, was more than one database used to identify cases? |
| • Is there a method for excluding cases originating from outside of the study population? | E.g. temporary residents or travellers from outside the population used as the denominator in the calculation of incidence. |
| • Is there a method for excluding pre-existing (prevalent) cases? | Is it explicitly stated that only new cases / cases diagnosed within the study period were included? |
| • Is there a method for avoidance of duplicate counting / reporting of cases? | In surveillance studies, were patient identifiers collected to distinguish duplicate reports? In studies ascertaining cases from multiple databases, were they linked or did the authors have access to patient identifiers? |
| • Are 95% confidence intervals for the incidence estimate reported, or can they be derived? | Confidence intervals could be derived if the number of incident cases, size of the denominator population, and study duration were reported. |

**Table 3.2** Assessment domains for risk of bias and external validity of included studies.

| Domain | Grading criteria |
|---|---|
| 1. Risk of case misclassification | Considered HIGH risk if any of the following:<br>- No case definition provided (unless the clinical presentation of cases is reported and is consistent with symptomatic vitamin D deficiency in ≥80%, when the risk is considered moderate).<br>- Case status not verified by review of medical notes or clinical assessment (based entirely upon diagnostic codes in healthcare / administrative databases).<br><br>Considered MODERATE risk if any of the following:<br>- 25-OH-D status not included in case definition, or not reported as being low among the majority of included cases (<50 nmol/l in ≥80% of cases).<br>- Children with predisposing chronic diseases (e.g. renal or liver disease, GI malabsorption) not excluded. Risks inclusion of cases where vitamin D deficiency is not the primary aetiology.<br>- Case definition not clear. |
| 2. Risk of case under-ascertainment | Considered HIGH risk if any of the following:<br>- Only includes children admitted to hospital (inpatients).<br>- Cases ascertained by retrospective clinician survey (as opposed to prospective surveillance).<br>- Response rate <70% (if applicable).<br>- Method of case ascertainment not described.<br><br>Considered MODERATE risk if any of the following:<br>- Only includes children presenting to secondary care (inpatient and outpatient), not primary care.<br>- Single source of case reporting for surveillance studies.<br>- Response rate ≥70%, but <80% (if applicable).<br>- Only includes cases with confirmed radiographic evidence of rickets (children diagnosed without radiographic evaluation will be missed). |
| 3. Reliability of the population at risk estimate | Considered to be HIGH if derived from reliable population estimates for a defined geographical area (e.g. census statistics), or if the study involved a research cohort of known size. The denominator estimate should also match in time with the period of case identification.<br><br>Considered to be LOW or MODERATE if the estimate is derived from data sources other than reliable population estimates, or if the time period for the population estimate does not match the period of case identification. Decision between grading of LOW or MODERATE based upon a subjective assessment of the risk of significant inaccuracy in the estimate of the population at risk. |
| 4. Generalisability to the national population | Considered HIGH for national studies that cover the entire target population within the country.<br><br>Considered MODERATE for regional studies that include the entire target population within a large / high-level administrative area (e.g. a state in the USA, or a county in the UK).<br><br>Considered LOW if the study population is not representative of the general population of children within a geographical region (e.g. it is limited to a single ethnic group, or to individuals registered with a particular healthcare provider), or for local studies that are limited to a relatively small geographical area (e.g. a single city, or a low-level administrative region). |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; GI, gastrointestinal.

### *3.3.7 Data Synthesis and Analysis*

Some of the included studies reported incidence estimates over a time period other than 1 year, in which case an annual incidence estimate was derived by dividing the reported incidence estimate by the duration of the study period in years. Incidence estimates were re-calculated per 100,000 children or person-years at risk, if not originally reported as such.

If a 95% confidence interval (CI) for the incidence estimate was not reported, but the relevant numerator and denominator values for the calculation of incidence were provided, a 95% confidence interval was calculated using the exact Poisson method.

One included study did not report an appropriately derived incidence estimate, but provided the number of incident cases of symptomatic vitamin D deficiency in a defined population for which a reliable population estimate was publicly available from an external source (El-Fakhri et al, 2013). In this case, an annual incidence risk estimate was calculated by dividing the total number of cases over the entire study period by the population estimate at the mid-point of the study, then further dividing by the duration of the study period in years. A 95% confidence interval for the incidence risk estimate was calculated using the exact Poisson method.

Incidence estimates from the included studies were displayed graphically using forest plots. Due to considerable heterogeneity among the included studies with respect to clinical and methodological aspects (see section 3.4.8), the estimation of pooled summary estimates was limited to studies considered to be of higher overall methodological quality (see section 3.3.6), and by necessity to studies for which 95% confidence intervals around incidence estimates were available. Random-effects models were used to calculate pooled incidence risk estimates, using the *metan* command in Stata (Sterne, 2009). Statistical evidence of heterogeneity between studies was assessed using chi-squared tests and the $I^2$ statistic (Higgins et al, 2003). The number of included studies was not sufficient to perform subgroup analysis to investigate possible sources of heterogeneity (calculation of pooled incidence estimates in strata of key variables such as geographical region or demographic characteristics of the study population), or meta-regression to examine and test differences in incidence rates in relation to socio-demographic factors.

Statistical and graphical analyses were performed using Stata MP version 14.2 (StataCorp, USA).

## 3.4 Results

### *3.4.1 Literature Search*

After the removal of duplicates, the literature search yielded a total of 8,299 citations (Figure 3.1). Following the initial screening of study titles and abstracts, 276 studies were selected for review of the full text. A further 9 potentially relevant studies for full text review were identified from the reference lists of included studies and relevant review articles. Following full text review, 13 studies that met the systematic review eligibility criteria were identified and included. One of these studies represents the publication of original data arising from work contributing to this thesis, and is described in full in chapter 4 (Basatemur & Sutcliffe, 2015).

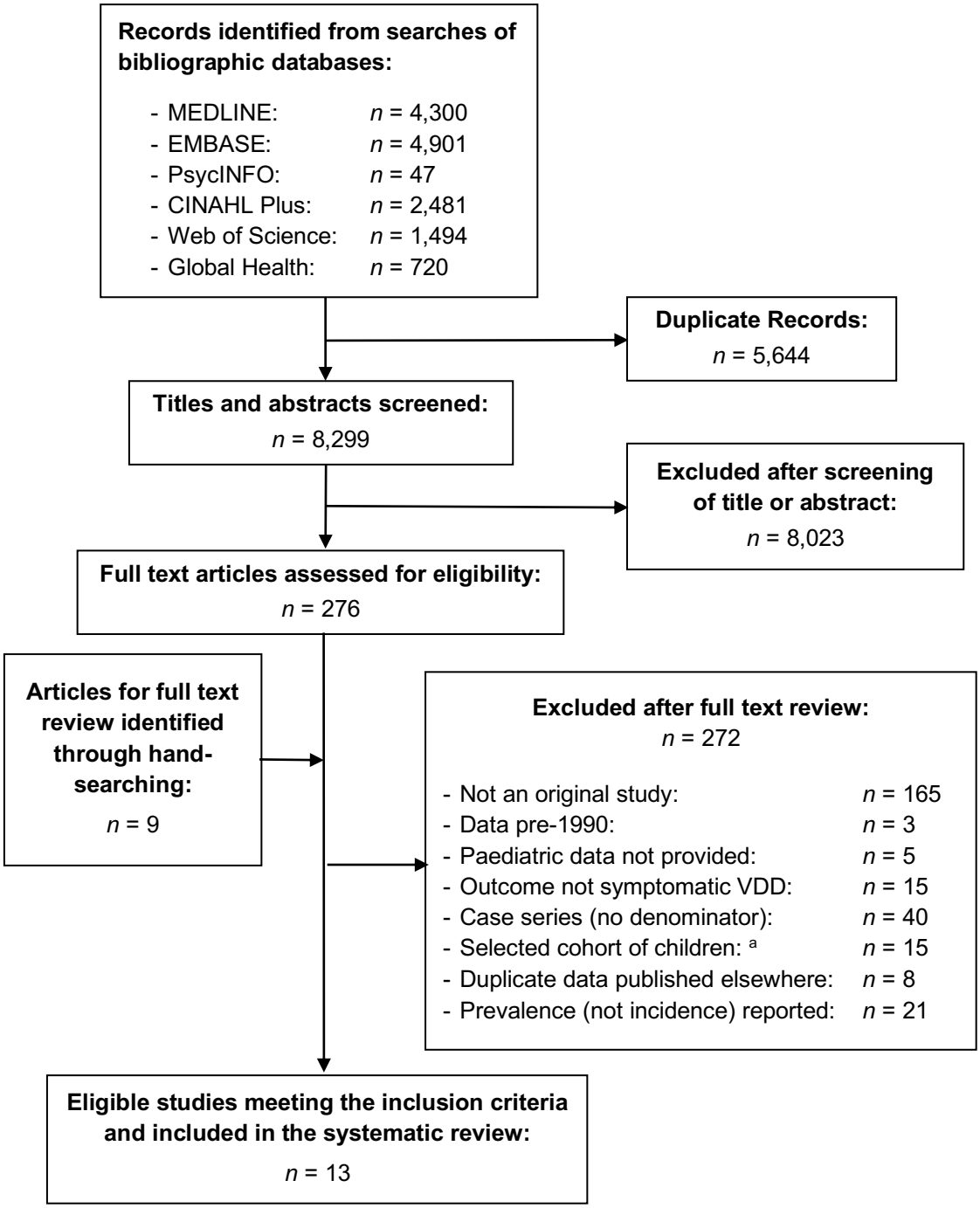
A prospective national surveillance study undertaken in Australia between January 2006 to July 2007, in which the reported outcome was the incidence of vitamin D deficiency rickets among children age 0 to 15 years, was excluded following review of the full text (Munns et al, 2012). Although the stated outcome was a clinical complication of vitamin D deficiency, the large majority of cases (>80%, exact number not provided) were identified through routine screening of vitamin D status undertaken at services such as refugee health clinics. The study case definition did not require the presence of any symptoms or signs attributable to vitamin D deficiency, and could be met on the basis of biochemical findings alone: i) serum 25-OH-D ≤50 nmol/l and ii) either a raised serum alkaline phosphatase level or radiological features of rickets. The study was therefore excluded, as the majority of cases represented biochemical vitamin D deficiency identified through the screening of asymptomatic individuals.

### *3.4.2 Characteristics of Included Studies*

Six of the studies reported data from Europe, 5 from North America, 1 from Asia, and 1 from New Zealand (Table 3.3). Five studies had national coverage, whilst eight were regional or local studies. The study methodology involved retrospective analysis of healthcare administrative data or hospital records in 7 studies, prospective surveillance through clinician reporting in 5 studies, and follow-up of children recruited to a non-randomised controlled trial in 1 study. The study outcome was stated as rickets in 9 studies, symptomatic vitamin D deficiency in 3 studies, and hypocalcaemic seizures secondary to vitamin D deficiency in 1 study. However, a number of the studies in

which the stated outcome was rickets also included children presenting with hypocalcaemic symptoms (Beck-Nielsen et al, 2009a; Thacher et al, 2013; Ward et al, 2007; Wheeler et al, 2015), making distinction difficult between studies reporting an incidence estimate specifically for rickets and those reporting an overall incidence estimate for any presentation of symptomatic vitamin D deficiency. Twelve studies reported an incidence risk estimate, whilst one study reported an incidence rate.

**Figure 3.1** Flow diagram outlining study selection and exclusion.




Abbreviations: VDD, vitamin D deficiency.
[a] The data was not drawn from a general population of children, for example where the study population was limited to children with a co-morbidity or those receiving healthcare services.

**Table 3.3** Characteristics and design of included studies with overall incidence rates, grouped by continent.

| Study [a] | Country & region | Study duration | Setting, population and age group | Study design & source of case ascertainment | Exclusion criteria | Stated outcome and case definition | Source & size of denominator data | No. of cases | Outcome measure, incidence estimate, & 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| ***Europe*** | | | | | | | | | |
| Callaghan, 2006 | England<br><br>West Midlands | 1 year, from May 2000 to April 2001 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–4 years | Prospective surveillance study of paediatricians in the West Midlands<br><br>Active case reporting by paediatricians every month | Prematurity | *Outcome:* Symptomatic vitamin D deficiency<br><br>*Case definition:*<br>1) Radiographic signs of rickets (fraying or splaying at end or a long bone)<br>OR<br>2) Hypocalcaemic convulsion thought to be caused by VDD | *Source:* Population statistics from 2001 census<br><br>*Size:* N/A | 24 | Incidence risk<br><br>7.5 per 100,000 children per year<br><br>95% CI: N/A |
| Beck-Nielsen, 2009 | Denmark<br><br>Southern Denmark | 11 years, from 1995 to 2005 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–14 years | Analysis of healthcare administrative data (Danish National Patient Registry and hospital registers)<br><br>Cases identified using ICD-8 (265, 265.0, 265.1, 265.9, 273.4) and ICD-10 (E55, E55.0, E55.9, E64.3, E83.3) codes for VDD & rickets | Renal insufficiency, renal tubular acidosis, liver / bile duct disease, genetic syndromes, medically induced rickets | *Outcome:* Nutritional rickets<br><br>*Case definition:*<br>1) 25-OH-D <25nmol/l and at least one of: raised ALP, raised PTH, or low $Ca^{2+}$ [b]<br>AND<br>2) Clinical or radiological signs of rickets [c]<br>AND<br>3) Rickets healed following treatment with vitamin D | *Source:* Population estimates from Statistics Denmark<br><br>*Size:* 246,972 (average yearly population size between 1995-2005) | 78 | Incidence risk<br><br>2.9 per 100,000 children per year<br><br>95% CI: 2.3 to 3.6 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; $Ca^{2+}$, calcium; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available; PTH, parathyroid hormone; VDD, vitamin D deficiency.

[a] First author, year of publication

[b] Where a 25-OH-D level was not available, cases included if at least one of the following present: raised ALP, raised PTH, or low $Ca^{2+}$

[c] In infants and young children, clinical signs of rickets defined as one of: craniotabes, rachitic rosary, Harrison groove, enlargement of wrists knees or ankles, bowing of weight bearing extremeties, or hypocalcaemic seizures. In adolescents, clinical signs defined as one of: enlargement of writsts, knees or ankles, bowing of legs, muscle weakness, pain of lower limbs or in the back, or hypocalcaemic seizures. Radiological signs defined as widening of growth plates with irregularity and cupping of their metaphyseal borders.

**Table 3.3** continued.

| Study [a] | Country & region | Study duration | Setting, population and age group | Study design & source of case ascertainment | Exclusion criteria | Stated outcome and case definition | Source & size of denominator data | No. of cases | Outcome measure, incidence estimate, & 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| ***Europe (continued)*** | | | | | | | | | |
| Moy, 2012 | England<br><br>Part of inner-city Birmingham (Heart of Birmingham Primary Care Trust catchment area) | 2 x 1-year periods:<br><br>1) Jan to Dec 2005<br><br>2) March 2009 to Feb 2010 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population resident in the Primary Care Trust catchment area<br><br>*Age:* 0–4 years | Retrospective analysis of medical records from 3 hospitals, before & after an intervention to increase vitamin D supplement uptake.<br><br>Cases identified by medical record review of all children with a 25-OH-D record <25 nmol/l | Chronic renal or hepatic disease, incidental finding of low 25-OH-D in an asymptomatic child | *Outcome:* Symptomatic vitamin D deficiency<br><br>*Case definition:*<br>1) 25-OH-D <25 nmol/l AND<br>2) Diagnosis of rickets, hypocalcaemic seizure, or muscle weakness (clinical outcomes not further defined) | *Source:* Population statistics from 2001 census<br><br>*Size:* N/A | *2005:* 29<br><br>*2009-2010:* 12 | Incidence risk<br><br>*Jan to Dec 2005:* 120 per 100,000 children per year<br><br>*March 2009 to Feb 2010:* 49 per 100,000 children per year<br><br>95% CIs: N/A |
| El-Fakhri, 2013 | Scotland<br><br>National study | 2 years, from Sept. 2009 to August 2011 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–16 years | Prospective surveillance study using the Scottish Paediatric Surveillance Unit network<br><br>Active case reporting by paediatricians every month | Osteopenia of prematurity, genetic or drug-induced rickets, liver disease, chronic renal insufficiency, malabsorption, thalassaemia | *Outcome:* Symptomatic vitamin D deficiency<br><br>*Case definition:* Symptoms or signs related to vitamin D deficiency or hypocalcaemia (not specified) | *Source:* Mid-2010 national population estimate (Office for National Statistics) [b]<br><br>*Size:* 981,072 | 109 | Incidence risk<br><br>5.6 per 100,000 children per year [b]<br><br>95% CI: 4.6 to 6.7 |
| Goldacre, 2014 | England<br><br>National study | 5 years, from 2007 to 2011 | *Setting:* Hospital admissions data (inpatient secondary care)<br><br>*Population:* General population<br><br>*Age:* 0–14 years | Analysis of healthcare administrative data (Hospital Episode Statistics)<br><br>Cases identified using ICD-10 code for 'active rickets' | None | *Outcome:* Rickets<br><br>*Case definition:* Record of ICD-10 code E55.0 ('active rickets') | *Source:* Not stated, but likely to be national population estimates<br><br>*Size:* N/A | Not stated | Incidence risk - directly standardised to European standard population using 5-year age groups<br><br>3.16 per 100,000 children per year<br><br>95% CI: 3.00 to 3.33 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available.
[a] First author, year of publication
[b] A national incidence estimate was not reported by the authors, but has been calculated using the number of incident cases reported in the paper alongside publicly available national population estimates for Scotland from the Office for National Statistics (ONS, 2013c).

**Table 3.3** continued.

| Study [a] | Country & region | Study duration | Setting, population and age group | Study design & source of case ascertainment | Exclusion criteria | Stated outcome and case definition | Source & size of denominator data | No. of cases | Outcome measure, incidence estimate, & 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| ***Europe (continued)*** | | | | | | | | | |
| Basatemur, 2015 | UK & Ireland<br><br>National study | 2 years, from Sept. 2011 to Sept. 2013 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–15 years | Prospective surveillance study using the British Paediatric Surveillance Unit network<br><br>Active case reporting by paediatricians every month | Alternative cause of seizures present at time of event, chronic renal disease, total parenteral nutrition, liver disease, malabsorption, inherited disorder of vitamin D metabolism. | *Outcome:* Hypocalcaemic seizure secondary to VDD<br><br>*Case definition:*<br>1) Clinical seizure<br>AND<br>2) Serum $Ca^{2+}$ <2.0 mmol/l<br>AND<br>3) 25-OH-D <50 nmol/l | *Source:* 2012 national population estimates from the ONS and CSO<br><br>*Size:* 13,037,071 | 92 | Incidence risk<br><br>0.35 per 100,000 children per year<br><br>95% CI: 0.28 to 0.43 |
| ***North America*** | | | | | | | | | |
| CDC, 2001 | USA<br><br>Georgia | 18 months, from Jan 1997 to June 1999 | *Setting:* Hospital admissions data (inpatient secondary care)<br><br>*Population:* General population resident in Georgia<br><br>*Age:* 6 months to 5 years | Retrospective analysis of discharge records from hospitals in Georgia<br><br>Cases identified using ICD-9 codes for rickets (268.0), vitamin D deficiency (268.9), or osteomalacia (268.2) | Congenital or genetic aetiology, premature birth, chronic diseases (N/S) | *Outcome:* Vitamin D deficiency rickets<br><br>*Case definition:*<br>1) 25-OH-D level below lab reference range (N/S)<br>AND<br>2) Radiographic signs: osteopenia, growth plate widening, fraying/cupping of metaphysis, craniomalacia | *Source:* Population census data for the State of Georgia<br><br>*Size:* N/A | 6 | Incidence risk<br><br>0.3 per 100,000 children per year<br><br>95% CI: N/A |
| Ward, 2007 | Canada<br><br>National Study | 2 years, from July 2002 to June 2004 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–18 years | Prospective surveillance study using the Canadian Paediatric Surveillance Program network<br><br>Active case reporting by paediatricians every month | Liver disease, total parenteral nutrition, renal insufficiency, genetic disorder of vitamin D metabolism, fat malabsorption | *Outcome:* Vitamin D deficiency rickets<br><br>*Case definition:*<br>No definition of rickets specified. Serum 25-OH-D <27.5 nmol/l specified as an inclusion criteria. | *Source:* 2003 national population estimates from Statistics Canada<br><br>*Size:* N/A | 104 | Incidence risk<br><br>2.9 per 100,000 children per year<br><br>95% CI: 2.2 to 3.7 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; $Ca^{2+}$, calcium; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CSO, Central Statistics Office Ireland; ICD, International Classification of Diseases; N/A, not available; N/S, not specified; ONS, Office for National Statistics; VDD, vitamin D deficiency

[a] First author, year of publication

**Table 3.3** continued.

| Study [a] | Country & region | Study duration | Setting, population and age group | Study design & source of case ascertainment | Exclusion criteria | Stated outcome and case definition | Source & size of denominator data | No. of cases | Outcome measure, incidence estimate, & 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| ***North America (continued)*** | | | | | | | | | |
| Thacher, 2013 | USA<br><br>Olmsted County, Minnesota | 2 x 10-year periods: 1990 to 1999, and 2000 to 2009 | *Setting:* Primary and secondary care<br><br>*Population:* General population resident in Olmsted county<br><br>*Age:* 0–2 years | Analysis of linked healthcare administrative data (Rochester Epidemiology Project)<br><br>Cases identified using codes for: rickets, vitamin D deficiency, osteomalacia, genu varum/valgum, tetany, craniotabes, hypocalcaemia, angulation, hypocalcaemic seizure, chest deformity | Inherited / genetic cause of rickets, renal tubular disorders, renal insufficiency, tumor-induced osteomalacia, hypophosphatasia | *Outcome:* Nutritional rickets<br><br>*Case definition:* Radiographic interpretation consistent with rickets (not specified) and no evidence of non-nutritional causes of rickets | *Source:* Rochester Epidemiology Project cohort population<br><br>*Size:* N/A | *1990-1999:* 2<br><br>*2000-2009:* 14 | Incidence rate<br><br>*1990-1999:* 3.7 per 100,000 person-years<br>95% CI: N/A<br><br>*2000-2009:* 24.1 per 100,000 person-years<br>95% CI: N/A |
| Millette, 2014 | Canada<br><br>Quebec | 2 separate 1-year periods: 2004 & 2009 | *Setting:* Primary and secondary care<br><br>*Population:* Children covered by a public medication insurance plan<br><br>*Age:* 0–6 years | Analysis of linked data from 2 healthcare administrative databases and the state birth registry (the Quebec Pregnancy Cohort)<br><br>Cases identified using ICD codes for rickets or vitamin D deficiency. | Inherited forms of rickets, renal failure, born at <37 or >42 weeks gestation, child or mother taking calcitriol | *Outcome:* Rickets<br><br>*Case definition:* Record of ICD-9 code 268 or ICD-10 code E55 | *Source:* Quebec Pregnancy Cohort population<br><br>*Size:*<br>*2004:* ~100,000<br>*2009:* ~83,000 | *2004:* 3<br><br>*2009:* 6 | Incidence risk<br><br>*2004:* 3.0 per 100,000 children<br>95% CI: 0.6 to 8.8<br><br>*2009:* 7.2 per 100,000 children<br>95% CI: 2.7 to 15.7 |
| Singleton, 2015 | USA<br><br>Alaska | 15 years, from 1999 to 2013 | *Setting:* Inpatient and outpatient data from health facilities for Alaska native people<br><br>*Population:* Alaska native (American Indian) children<br><br>*Age:* 0–9 years | Analysis of healthcare administrative data (Indian Health Service National Patient Information Reporting System [IHS]).<br><br>Cases identified using ICD-9 codes for rickets (268.1, 268.0) & vitamin D deficiency (268.9), and lab records for 25-OH-D <37.5 nmol/l. | Rickets associated with hepatic disease or malabsorption | *Outcome:* Nutritional rickets<br><br>*Case definition:*<br>1) 25-OH-D <37.5 nmol/l AND<br>2) Recorded clinical or radiographic signs consistent with rickets (not specified) | *Source:* The IHS user population, calculated as the number of individuals who received any IHS-funded care in the preceding 3 years.<br><br>*Size:* N/A | 16 | Incidence risk<br><br>4.2 per 100,000 children per year<br><br>95% CI: N/A |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available.
[a] First author, year of publication

**Table 3.3** continued.

| Study [a] | Country & region | Study duration | Setting, population and age group | Study design & source of case ascertainment | Exclusion criteria | Stated outcome and case definition | Source & size of denominator data | No. of cases | Outcome measure, incidence estimate, & 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| ***Asia*** | | | | | | | | | |
| Beser, 1994 | Turkey<br><br>Akcaabat district (in Trabzon province, northeast Turkey) | 12 months follow-up per child, during the period 1990-1992 | *Setting:* Control arm of intervention study<br><br>*Population:* Children from 21 villages attached to a single health centre<br><br>*Age:* 3 to 36 months | Non-randomised study of vitamin D supplementation vs no intervention.<br><br>Physical examination by study investigators and unspecified biochemical and radiological tests, 12 months after recruitment | Rickets present at baseline | *Outcome:* Rickets<br><br>*Case definition:* None. | *Source:* Number of children in no intervention arm of the study<br><br>*Size:* 369 | 14 | Incidence risk<br><br>3,800 per 100,000 children (3.8%)<br><br>95% CI: 2,074 to 6,366 |
| ***Oceania*** | | | | | | | | | |
| Wheeler, 2015 | New Zealand<br><br>National study | 3 years, from July 2010 to June 2013 | *Setting:* Secondary care (inpatient and outpatient)<br><br>*Population:* General population<br><br>*Age:* 0–14 years | Prospective surveillance study using the New Zealand Paediatric Surveillance Unit network<br><br>Active case reporting by paediatricians every month | Fat malabsorption, liver disease, renal insufficiency, genetic forms of rickets, total parenteral nutrition | *Outcome:* Vitamin D Deficiency Rickets<br><br>*Case definition:*<br>1) 25-OH-D <50 nmol/l AND<br>2) Elevated ALP or radiological signs of rickets | *Source:* National census data for 2013 (Statistics New Zealand)<br><br>*Size:* 870,378 | 58 | Incidence risk<br><br>2.2 per 100,000 children per year<br><br>95% CI: 1.4 to 3.5 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; CI, confidence interval.
[a] First author, year of publication

### *3.4.3 Summary of Included Studies*

A summary of the study design and overall incidence rates reported by each of the included studies is given in Table 3.3. Assessment of the quality of study reporting and design is shown in Table 3.4. Assessment of the risk of bias, generalisability to the national population, and a description of the key limitations for each study is given in Table 3.5. A brief discussion of each of the included studies, grouped by geographical region, is given below.

#### *3.4.3.1 Europe*

Five studies were conducted in the United Kingdom (3 in England, 1 in Scotland, and 1 study across the UK and Ireland), and one in Denmark.

A prospective surveillance study in the West Midlands region of England, involving active case reporting by paediatricians, identified 24 cases of symptomatic vitamin D deficiency among children aged 0 to 4 years presenting to secondary care over a one year period between May 2000 to April 2001 (Callaghan et al, 2006). Children met the case criteria if they had radiographic features of rickets or presented with a hypocalcaemic seizure where the most likely cause was considered to be vitamin D deficiency by the treating clinician. This equated to an overall annual incidence risk of 7.5 per 100,000 children aged 0 to 4 years. The incidence risk was considerably higher among children from South Asian (38 per 100,000) and black (95 per 100,000) ethnic backgrounds than among those of white ethnic origin (0.4 per 100,000). Confidence intervals around the incidence estimates were not reported, and would be expected to be relatively wide given the small number of cases. Case ascertainment was limited to children presenting to secondary care, and there was a non-response rate of 24% for requests to report cases. Although vitamin D status was not explicitly incorporated into the case definition, the authors state that all included children exhibited a biochemical profile consistent with vitamin D deficiency, without elaborating further. Regional differences in ethnic demography limit the generalisability of the findings to the UK as a whole: the West Midlands has a higher South Asian population than the national average (12.3% compared to 6.7% nationally in England & Wales, among children aged 0 to 4 years in the 2001 Census) (ONS, 2001).

**Table 3.4** Assessment of the quality of study reporting and methodology for included studies.

| Study (first author, year) | Study population clearly defined? | Entire population survey, or random sample from the general population? | Clear inclusion and exclusion criteria? | Study time period clearly specified? | Case definition clearly specified? | Case definition includes assessment of vitamin D status? | Cases ascertained or validated using clinical review or medical notes? | Response rate (for studies involving primary data collection) | Multiple sources used for case ascertainment? | Method for excluding cases originating outside of the population? | Method for exclusion of prevalent cases? | Method for avoidance of duplicate counting of cases / reports? | 95% CI reported or derived? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Basatemur, 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 93% | No | Yes | Yes | Yes | Reported |
| Beck-Nielsen, 2009 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes | Yes | Yes | Derived |
| Beser, 1994 | Yes | No | Yes | Yes | No | No | Yes | 98.6% | No | Yes | Yes | Yes | Derived |
| Callaghan, 2006 | Yes | Yes | Yes | Yes | Yes | No | Yes | 76% | No | No | Unclear | Yes | No |
| CDC, 2001 | Yes | Yes | Partial | Yes | Partial | Threshold not specified | Yes | N/A | No | Yes | Unclear | Yes | No |
| El-Fakhri, 2013 | Yes | Yes | Yes | Yes | No | No | Yes | Not reported | No | Unclear | Yes | Yes | Derived |
| Goldacre, 2014 | Yes | Yes | Yes | Yes | Yes | No | No | N/A | No | No | Yes | Yes | Reported |
| Millette, 2014 | Yes | No | Partial | Yes | Yes | No | No | N/A | Yes | Yes | Yes | Yes | Derived |
| Moy, 2012 | Yes | Yes | Yes | Yes | Partial | Yes | Yes | N/A | No | Yes | Yes | Yes | No |
| Singleton, 2015 | Yes | No | Yes | Yes | Partial | Yes | Yes | N/A | Yes | Yes | Yes | Yes | No |
| Thacher, 2013 | Yes | Yes | Yes | Yes | Partial | No | Yes | N/A | Yes | Yes | Yes | Yes | No |
| Ward, 2007 | Yes | Yes | Yes | Yes | No | Yes | Yes | 84.5% | No | Yes | Yes | Yes | Reported |
| Wheeler, 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 92% | No | Unclear | Yes | Yes | Reported |

Abbreviations: N/A, not applicable.

**Table 3.5** Assessment of the risk of bias, external generalisability, and summary of the main limitations for included studies.

| Study | Risk of case misclassification | Risk of case under-ascertainment | Reliability of population at risk estimate | Generalisability to national population | Notes regarding study limitations |
|---|---|---|---|---|---|
| Basatemur, 2015 | Low | Moderate | High | High | - Single source of case ascertainment<br>- Case status could not be ascertained for 7% of case reports |
| Beck-Nielsen, 2009 | Low | Moderate | High | Moderate | - Only includes cases presenting to secondary care<br>- Cases ascertained using only diagnostic codes in administrative databases<br>- Regional study |
| Beser, 1994 | High | Low | High | Low | - No case definition for rickets specified, left to study investigator judgement<br>- High risk that case inclusion was based on non-specific clinical signs<br>- Assessment of vitamin D status not incorporated in the case definition<br>- No exclusion of children with predisposing chronic diseases<br>- Small study size, and large statistical uncertainty in incidence estimate<br>- Covers a limited geographical region |
| Callaghan, 2006 | Moderate | Moderate | High | Moderate | - No exclusion of children with predisposing chronic diseases<br>- Assessment of vitamin D status not incorporated in the case definition<br>- Not explicitly stated that prevalent cases were excluded<br>- Single source of case ascertainment<br>- Only includes cases presenting to secondary care (paediatricians)<br>- Non-response rate of 24%<br>- Regional study<br>- Confidence intervals not reported and cannot be derived |
| CDC, 2001 | Moderate | High | High | Moderate | - 25-OH-D level considered low not defined<br>- Not explicitly stated that prevalent cases were excluded<br>- Only includes cases requiring hospital admission<br>- Cases ascertained using only diagnostic codes in administrative databases<br>- Case inclusion limited to children with confirmed radiographic signs<br>- Regional study<br>- Confidence intervals not reported and cannot be derived |
| El-Fakhri, 2013 | Moderate | Moderate | High [a] | High [a] | - Clinical symptoms / signs used to determine case inclusion not defined<br>- Assessment of vitamin D status not incorporated in the case definition<br>- Only includes cases presenting to secondary care (paediatricians)<br>- Single source of case ascertainment |
| Goldacre, 2014 | High | High | High | High | - Cases ascertained using only diagnostic codes in administrative databases<br>- Case status not verified by review of medical notes<br>- Assessment of vitamin D status not incorporated in the case definition<br>- No exclusion of children with predisposing chronic diseases<br>- Only includes cases requiring hospital admission |

**Table 3.5** continued.

| Study | Risk of case misclassification | Risk of case under-ascertainment | Reliability of population at risk estimate | Generalisability to national population | Notes regarding study limitations |
|---|---|---|---|---|---|
| Millette, 2014 | High | Moderate | High | Low | - Cases ascertained using only diagnostic codes in administrative databases<br>- Case status not verified by review of medical notes<br>- Assessment of vitamin D status not incorporated in the case definition<br>- Study population limited to individuals eligible for a public medical insurance plan – may not be representative of the general population<br>- Small number of cases & large statistical uncertainty in incidence estimate |
| Moy, 2012 | Low | Moderate | Moderate | Low | - Clinical outcomes used to determine case inclusion not fully defined<br>- Only includes cases with 25-OH-D <25 nmol/l, children with higher 25-OH-D levels or who received treatment prior to testing will be excluded<br>- Only includes cases presenting to secondary care<br>- Estimate for population at risk does not match study time period<br>- Covers a limited geographical region, with a marked difference in ethnic demography compared to the national population.<br>- Confidence intervals not reported and cannot be derived |
| Singleton, 2015 | Moderate | Moderate | Low | Low | - High risk that denominator data does not accurately reflect the population at-risk; derived from users of healthcare services, not true population estimates<br>- Limited to a single ethnic group (American Indian Alaska native)<br>- Limited to cases treated at Indian Health Service funded providers<br>- Confidence intervals not reported and cannot be derived<br>- Clinical signs of rickets used to determine case inclusion not defined |
| Thacher, 2013 | High | High | High | Low | - Assessment of vitamin D status not incorporated in the case definition<br>- Radiological signs of rickets used to determine case inclusion not defined<br>- Case inclusion limited to children with confirmed radiographic features of rickets, any cases diagnosed without radiographic evaluation not included<br>- Covers a limited geographical region<br>- Confidence intervals not reported and cannot be derived |
| Ward, 2007 | Moderate | Moderate | High | High | - No case definition of rickets specified, left to individual clinician judgement.<br>- Single source of case ascertainment<br>- Only includes cases presenting to secondary care (paediatricians) |
| Wheeler, 2015 | Low | Moderate | High | High | - Single source of case ascertainment<br>- Only includes cases presenting to secondary care (paediatricians) |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CDC, Centers for Disease Control and Prevention; ICD, International Classification of Diseases.
[a] Assessment relates to the calculation of incidence performed using national population estimates for Scotland available from the Office for National statistics, not to the analyses reported in the paper.

A local study in inner-city Birmingham, a city in the West Midlands region of England, investigated the incidence of symptomatic vitamin D deficiency in children presenting to secondary care, before and after a local public health initiative in 2005 to provide universal free of charge vitamin D supplements to pregnant and lactating women and children aged under 5 years (Moy et al, 2012). Cases were identified through the retrospective analysis of medical records from 3 local hospitals. Children met the case criteria if aged 0 to 4 years, with a 25-OH-D level <25 nmol/l, and a clinical diagnosis of either rickets, hypocalcaemic seizure or muscle weakness. 29 cases were identified in 2005, and 12 cases in a separate 12-month period between March 2009 to February 2010. This equated to an annual incidence risk of 120 per 100,000 children aged 0 to 4 years in 2005, and 49 per 100,000 children in 2009-2010. However, caution must be taken in drawing conclusions about temporal trends from this data, as confidence intervals were not provided and incidence was reported from two distinct 1-year time periods as opposed to continuous time-trend data. The authors report that 75% of the population of inner-city Birmingham were from ethnic minority groups (compared to 9% nationally across England and Wales in 2001), which prevents generalisability of the results to the national population, and is the most likely explanation for the incidence figures being considerably higher than those reported by other studies in Europe and North America (Table 3.3). The ethnic origin of cases was not reported.

A prospective surveillance study in Scotland, involving active case reporting by paediatricians on a monthly basis, identified 109 cases of symptomatic vitamin D deficiency among children aged 0 to 16 years presenting to secondary care over a two year period between September 2009 to August 2011 (El-Fakhri et al, 2013). Clinicians were asked to report children with symptoms or signs related to vitamin D deficiency or hypocalcaemia, however an important limitation of the study was the absence of a case definition for validation of reported cases. Information about clinical presentation was available for 90% of cases (n=98), of whom 85% (n=83) had a presentation consistent with symptomatic vitamin D deficiency (bone deformity, gait abnormality, bone pain, fracture, or hypocalcaemic seizure). Although the surveillance had national coverage, the authors did not report national incidence estimates. They attempted to derive separate incidence estimates for the two major cities in Scotland (Glasgow and Edinburgh), where the majority of cases (90%) had been reported from (82 from Glasgow, 16 from Edinburgh). They used population estimates for children resident in these cities as the denominator for the calculations, and reported incidence estimates of 80 per 100,000 children aged 0 to 16 in Glasgow, and 19 per 100,000 children in Edinburgh. However, it is unlikely that children who receive secondary care in hospitals in these cities will be restricted to children who reside there, as children who live

outside of Glasgow or Edinburgh could be referred to these hospitals for specialist care. Data regarding area of residence or postcode was not collected, and therefore the city-based incidence estimates may include cases from outside the denominator populations. Furthermore, the ethnic demography of Glasgow and Edinburgh differs considerably from that of Scotland as a whole; nationally 5.6% of children aged 0 to 17 years were of non-white ethnicity in the 2011 Scottish census, compared to 11.6% of children in Edinburgh and 17.9% of children in Glasgow (NRS, 2014). The authors do not provide an explanation for why they reported city-based rather than national incidence estimates. For the purpose of this systematic review, the number of incident cases reported nationally (as stated in the paper) was used alongside mid-2010 national population estimates available from the Office for National Statistics (ONS, 2013c), to derive an annual incidence risk estimate of 5.6 per 100,000 children aged 0 to 16 across Scotland (95% CI: 4.6 to 6.7). Case ascertainment was limited to children presenting to secondary care, and the response rate from clinicians for requests to report cases was not reported. Data regarding serum 25-OH-D level was missing for 24% of cases. Among cases with data available, 25-OH-D levels were ≤25 nmol/l for 83%, between 26-50 nmol/l for 14%, and >50 nmol/l for 2%. 53% of cases were of South Asian ethnic origin, 26% African, 9% Middle Eastern, and 9% white.

An analysis of routinely collected Hospital Episode Statistics data in England identified hospital admissions among children in which the coded diagnosis was 'active rickets' (Goldacre et al, 2014). Following direct standardisation by age to the European Standard Population, the annual incidence risk between 2007 to 2011 was reported to be 3.16 per 100,000 children aged 0 to 14 (95% CI: 3.00 to 3.33). An important limitation of the study is that only cases admitted to hospital as inpatients were ascertained, whilst many children with rickets will be managed as outpatients. The risk of case misclassification was considered to be high as case status was determined using administrative codes only with no validation of case status through review of medical records, and children with predisposing chronic conditions or inherited causes of rickets were not excluded. Among cases for whom ethnicity data was available, 33% were reported to be of South Asian origin, 33% black, and 32% white, although the authors acknowledged that the overall recording of ethnicity data was poor.

A prospective surveillance study of hypocalcaemic seizures secondary to vitamin D deficiency, undertaken across the UK and Ireland between September 2011 to September 2013, is described in full in chapter 4 (Basatemur & Sutcliffe, 2015). The overall annual incidence risk was 0.35 per 100,000 children aged 0 to 15 years (95% CI: 0.28 to 0.43).

A retrospective cohort study in Southern Denmark used diagnostic codes for vitamin D deficiency and rickets to identify children with possible nutritional rickets from hospital records and a national healthcare administrative database (the Danish National Patient Registry), which included both inpatient and outpatient data (Beck-Nielsen et al, 2009a). The medical records of potential cases were reviewed, and children were included if they met a clearly described case definition that required biochemical as well as clinical or radiographic evidence of symptomatic vitamin D deficiency, and clinical improvement following treatment with vitamin D (see Table 3.3). Seventy-eight children met the case criteria over an 11-year period between 1995 to 2005, corresponding to an overall annual incidence risk of 2.9 per 100,000 children aged 0 to 14 years (95% CI: 2.3 to 3.6). The incidence risk among children from immigrant backgrounds was considerably higher than the overall incidence, at 60 per 100,000 children aged 0 to 14 years (95% CI: 41 to 84). The incidence risk was also higher among younger children aged 0 to 2 years, at 5.8 per 100,000 children (95% CI: 4.0 to 8.3), than the overall incidence among children aged 0 to 14 years. Case ascertainment was limited to children managed in secondary care.

#### *3.4.3.2 North America*

Three studies were conducted in the United States of America, and two in Canada.

A retrospective analysis of hospital discharge records in the US state of Georgia identified 6 children aged between 6 months to 5 years who were admitted to hospital with vitamin D deficiency rickets over an 18 month period between January 1997 to June 1999 (CDC, 2001). Children met the case criteria if they had a serum 25-OH-D level below the local laboratory reference range (not specified) and radiographic signs of rickets. This equated to an annual incidence risk of 0.3 per 100,000 children aged between 6 months to 5 years. Insufficient information was provided to derive a confidence interval around the incidence estimate, however this would be expected to be wide given the small number of cases. A major limitation of the study was that only cases admitted to hospital as inpatients were ascertained, whilst many children with rickets would be expected to be managed as outpatients. Case ascertainment was also limited to children who had radiographic features of rickets, therefore any children diagnosed on the basis of clinical and biochemical features alone, without radiographic evaluation, would not have been included. The ethnic origin of cases was not reported.

A local retrospective cohort study conducted in Olmsted County in the US state of Minnesota, which had a total population of 145,225 in 2009, investigated the incidence of nutritional rickets among children aged 0 to 2 years, using data held in the Rochester Epidemiology Project (Thacher et al, 2013). The database contains linked medical records from 2 large integrated health systems, which between them cover 98% of all primary and secondary health care services for Olmsted County residents. Children were included as cases if they had radiographic evidence of rickets, in the absence of non-nutritional causes of rickets (predisposing chronic medical conditions and inherited causes of rickets). Two cases were identified between 1990 to 1999, and 14 cases between 2000 to 2009. This equated to an annual incidence rate of 3.7 per 100,000 person-years between 1990 to 1999, and 24.1 per 100,000 person-years between 2000 to 2009. Confidence intervals around the incidence estimates were not reported, and would be expected to be wide given the small numbers of cases, limiting conclusions that can be drawn regarding temporal trends. However, the authors speculate that an increase in the non-white, particularly Somali, immigrant population in the region during the study period may be a contributing factor to changing incidence over time. A strength of the study was the ascertainment of cases from both primary and secondary care. However, case ascertainment was limited to children who had radiographic features of rickets, therefore any children diagnosed on the basis of clinical and biochemical features alone, without radiographic evaluation, would not have been included. Vitamin D status was not incorporated into the case definition, and the range of serum 25-OH-D values reported among cases was wide (10 to 137 nmol/l), suggesting that an alternative aetiology to vitamin D deficiency (for example dietary calcium deficiency) may have been responsible in some cases. 59% of cases were of black ethnic origin, with 24% white, and 12% of mixed ethnic origin.

A retrospective cohort study in the US state of Alaska investigated the incidence of nutritional rickets among Alaska native American Indian children, using data held in the Indian Health Service (IHS) National Patient Information Reporting System (NIPRS) database (Singleton et al, 2015). The NIPRS contains data regarding all inpatient and outpatient activity in healthcare facilities for people of Alaska native American Indian origin. Children aged between 0 to 9 years met the case criteria if they had a serum 25-OH-D level <37.5 nmol/l, and either clinical features or radiographic signs consistent with rickets. 16 cases were identified over a 15-year study period between 1999 to 2013. The authors calculated an annual incidence risk of 4.2 per 100,000 children aged 0 to 9 years, however a confidence interval around this estimate was not provided. The denominator estimates used for the population at risk in each year are likely to be unreliable, as they were based on the numbers of children who had used IHS-funded

healthcare services in the preceding 3 years rather than true population estimates. The results are not generalisable to the general population, as the study was limited to children from a single ethnic group.

A national prospective surveillance study in Canada, involving active case reporting by paediatricians on a monthly basis, identified 104 cases of vitamin D deficiency rickets among children aged 0 to 18 years presenting to secondary care over a 2-year period between July 2002 to June 2004 (Ward et al, 2007). This equated to an annual incidence risk of 2.9 per 100,000 children aged 0 to 18 years. Children were included if they had a serum 25-OH-D level <27.5 nmol/l. A clear case definition for rickets was not provided, however >90% of cases were reported to have a clinical presentation consistent with symptomatic vitamin D deficiency (skeletal deformity, hypocalcaemic seizure, delayed developmental milestones, fracture, failure to thrive, or muscle weakness). Annual incidence estimates were stratified by age group as follows: 9 per 100,000 children aged <1 year (95% CI: 6 to 12), 12 per 100,000 children aged 1 to 2 years (95% CI: 8 to 16), and 0.3 per 100,000 children aged 3 to 7 years (95% CI: 0.1 to 0.7). Case ascertainment was limited to children presenting to secondary care. 33% of cases were of black ethnic origin, 25% from First Nations or Inuit indigenous backgrounds, 14% Middle Eastern, and 11% Caucasian.

A retrospective cohort study in the Canadian province of Quebec reported the incidence of rickets among children covered by a public medication insurance plan, in two separate 1-year periods (2004 and 2009) (Millette et al, 2014). This programme covered approximately 30% of pregnant women in Quebec and their children, encompassing recipients of social assistance and individuals without private insurance. Data for the cohort was held in the Quebec Pregnancy Cohort, which links birth and death registration data with two healthcare administrative databases containing information regarding diagnoses made in primary and secondary care. Cases were defined as children aged 0 to 6 years with a diagnostic code for vitamin D deficiency or rickets. Three cases were identified in 2004, and 6 cases in 2009. This equated to an annual incidence estimate of 3.0 per 100,000 children aged 0 to 6 years in 2004 (95% CI: 0.6 to 8.8), and 7.2 per 100,000 children in 2009 (95% CI: 2.7 to 15.7). The study had a number of significant limitations. The risk of case misclassification was considered to be high as case status was determined using administrative codes only, with no validation of case status through review of medical records. In view of the small numbers of cases, there is a large degree of statistical uncertainty around the incidence estimates. The vitamin D status of cases was not reported. The study population was a selected subgroup, rather than a random sample, of the general

population. The study population has been shown to have a lower average socio-economic position than the general population of Quebec, and the ethnic distribution of the population was not reported. The generalisability of the results to the national population is therefore questionable. The ethnic origin of cases was not reported.

#### *3.4.3.3 Asia*

A non-randomised interventional study, undertaken in the Trabzon province of northeast Turkey between 1990 to 1992, reported the incidence of rickets among children aged between 3 to 36 months who either received vitamin D supplementation (400 International Units per day) or no intervention for 12 months (Beser & Cakmakci, 1994). Children were recruited from 21 villages in a single district. Those found to have signs of rickets on physical examination at baseline were excluded. The investigators reported that 14 children out of 369 (3.8%) in the control arm of the study had signs of rickets on physical examination when followed-up at 12 months. This equates to an annual incidence risk of 3,800 per 100,000 children aged 3 to 36 months (95% CI: 2,074 to 6,366). A major limitation of the study was the absence of a case definition for the outcome, which was left to the investigators judgement. The authors did not report the clinical features of rickets among the cases identified during follow-up. However, they did report the most common symptoms and signs which prompted a diagnosis of rickets among children at baseline, which were: teeth disorders, craniotabes, delayed fontanelle closure, sweating of the head, and restlessness. None of these symptoms are specific for rickets, and the relevance of symptoms such as sweating of the head and restlessness are questionable. The authors state that suspected cases had laboratory and radiological investigations performed, but provide no further details of the investigations undertaken or the results. There is a very high risk of case misclassification, as children are likely to have been given a diagnosis of rickets on the basis of non-specific and vague clinical features.

#### *3.4.3.4 Oceania*

A national prospective surveillance study in New Zealand, involving active case reporting by paediatricians on a monthly basis, identified 58 cases of vitamin D deficiency rickets among children aged 0 to 14 years presenting to secondary care over a 3-year period between July 2010 to June 2013 (Wheeler et al, 2015). Children met the case criteria if they had a serum 25-OH-D level <50 nmol/l, and either an elevated serum alkaline phosphatase level or radiographic features of rickets. This

equated to an overall annual incidence risk of 2.2 per 100,000 children aged 0 to 14 years (95% CI: 1.4 to 4.5). The majority of included cases presented with clinical features consistent with symptomatic vitamin D deficiency (skeletal deformity, poor growth, motor delay, hypocalcaemic seizures or tetany, bone pain, or cardiomyopathy). However, in approximately 10% of cases the diagnosis was made as an incidental finding, or following sibling screening. Incidence was considerably higher in younger children aged 0 to 2 years (10.5 per 100,000 children per year, 95% CI: 6.7 to 16.6) than in older children aged 3 to 14 years (0.1 per 100,000 children per year, 95% CI: 0.02 to 1.0). Case ascertainment was limited to children presenting to secondary care. The ethnicity of affected children was not reported.

### *3.4.4 Methodological Quality of Included Studies*

Assessment of the quality of study reporting and design is shown in Table 3.4. Assessment of the risk of bias, generalisability to the national population, and a description of the key limitations for each study is given in Table 3.5.
Six of the thirteen studies were considered to be at high risk of bias influencing the reported incidence estimates, due to either a high risk of misclassification of cases (Beser & Cakmakci, 1994; Goldacre et al, 2014; Millette et al, 2014; Thacher et al, 2013), a high risk of case under-ascertainment (CDC, 2001; Goldacre et al, 2014; Thacher et al, 2013), or low reliability of the population at risk estimate (Singleton et al, 2015). Five of the thirteen studies were considered to have low generalisability to the national population, either because they were local studies covering a low-level administrative region (Beser & Cakmakci, 1994; Moy et al, 2012; Thacher et al, 2013), or because the study population was a selected group that was unlikely to be representative of the general population in that region (Millette et al, 2014; Singleton et al, 2015).

Six of the thirteen studies were considered to be of higher overall methodological quality (Basatemur & Sutcliffe, 2015; Beck-Nielsen et al, 2009a; Callaghan et al, 2006; El-Fakhri et al, 2013; Ward et al, 2007; Wheeler et al, 2015). These studies were considered not to be at high risk of bias, and to have moderate or high generalisability to the national population.

Confidence intervals around the incidence estimates were only reported in four of the thirteen studies (Basatemur & Sutcliffe, 2015; Goldacre et al, 2014; Ward et al, 2007; Wheeler et al, 2015), whilst sufficient information was available to derive confidence

intervals in a further four studies (Beck-Nielsen et al, 2009a; Beser & Cakmakci, 1994; El-Fakhri et al, 2013; Millette et al, 2014). For the remaining five studies, insufficient information was provided for the calculation of confidence intervals (Callaghan et al, 2006; CDC, 2001; Moy et al, 2012; Singleton et al, 2015; Thacher et al, 2013).

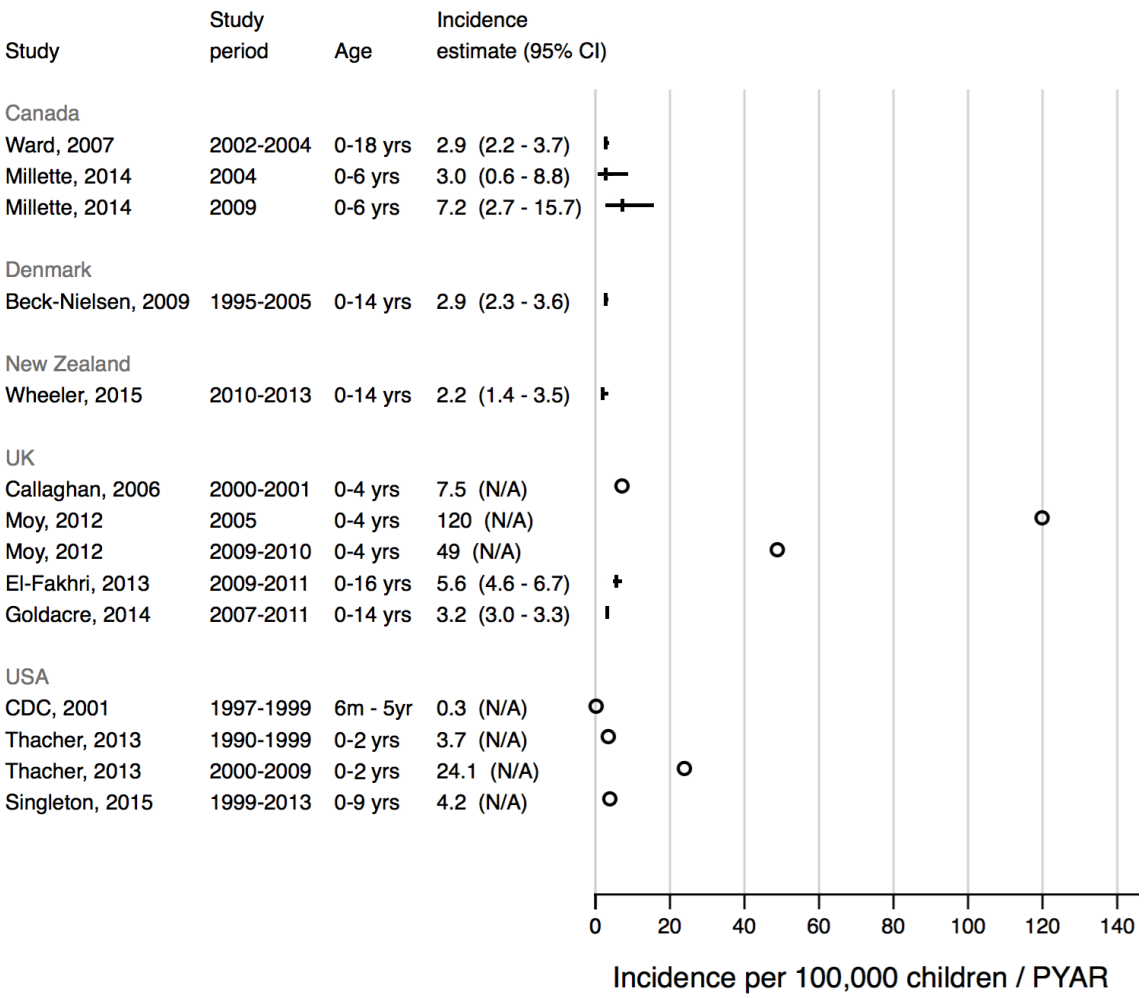
### *3.4.5 Overall Incidence Data*

Studies reporting a stated outcome of rickets or symptomatic vitamin D deficiency were considered together, as a number of the studies in which the stated study outcome was rickets also included children presenting with hypocalcaemic symptoms (Beck-Nielsen et al, 2009a; Thacher et al, 2013; Ward et al, 2007; Wheeler et al, 2015). The UK study specifically investigating hypocalcaemic seizures secondary to vitamin D deficiency was considered separately (Basatemur & Sutcliffe, 2015).

#### *3.4.5.1 Studies Reporting an Outcome of Rickets or Symptomatic Vitamin D Deficiency*

Figure 3.2 displays the incidence estimates from each of the included studies, with the exception of the small Turkish interventional study by Beser & Cakmakci (1994) which was excluded from the forest plot for purposes of clarity. The annual incidence risk for rickets reported by this study (3,800 per 100,000 children aged 3 to 36 months, 95% CI: 2,074 to 6,366) was over 30-fold higher than the next highest incidence estimate. As discussed in section 3.4.3.3, the risk of case misclassification in the Turkish study was considered to be very high, in view of the absence of a case definition and the diagnosis of rickets on the basis of non-specific and questionable symptoms and signs. Among the other included studies, annual incidence estimates for rickets or symptomatic vitamin D deficiency varied widely between 0.3 to 120 per 100,000 children.

**Figure 3.2** Forest plot of incidence estimates for rickets or symptomatic vitamin D deficiency, grouped by country of origin.[a]

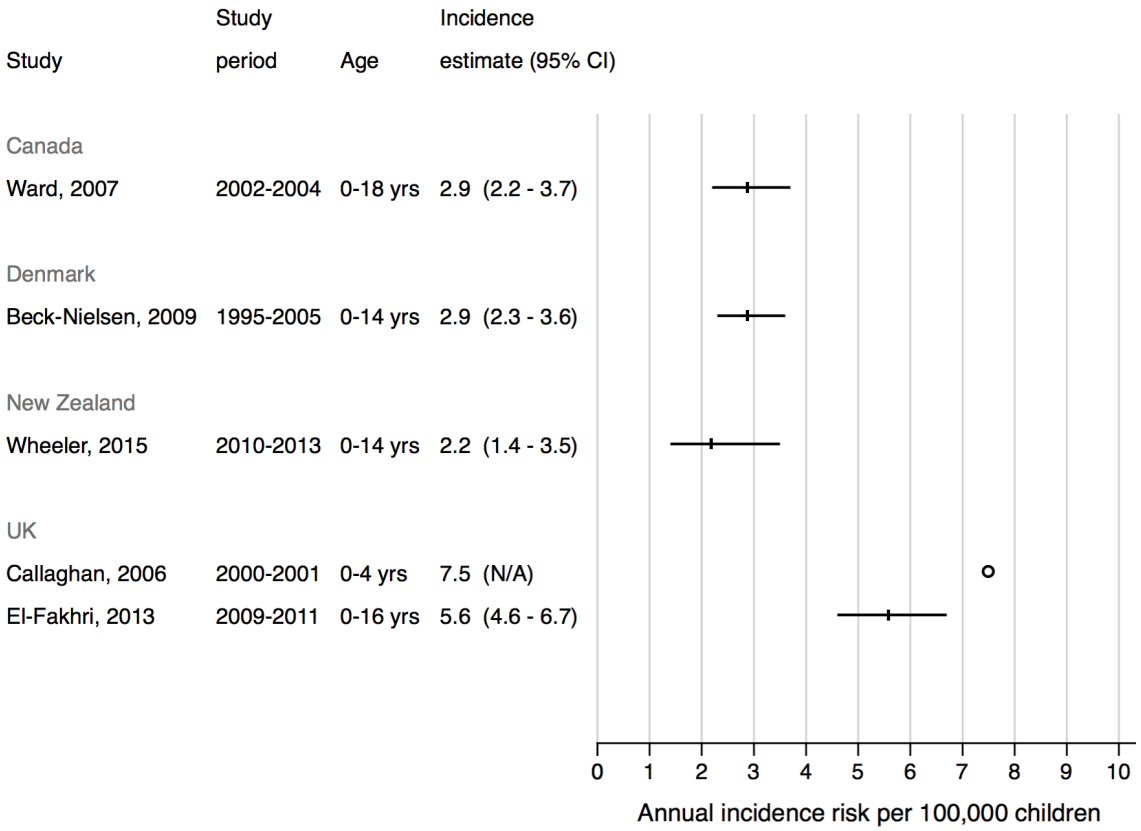



Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; m, months; N/A, not available; PYAR, person-years at risk; yrs, years.

[a] Overall incidence estimates from all included studies reporting an outcome of rickets or symptomatic vitamin D deficiency, with the exception of the study by Beser & Cakmakci (1994) which was excluded for purposes of clarity. The study time period and age of included children is also displayed for each study. Where studies report separate incidence estimates for more than one time period, each time period is displayed as a separate line. Estimates represent an annual incidence risk per 100,000 children for all studies, with the exception of Thacher et al (2013) where the estimates represent an incidence rate per 100,000 person-years at risk. Incidence estimates are represented by circles where 95% confidence intervals are not available.

When only the five studies considered to be of higher methodological quality were considered (see section 3.4.4), there was substantially less variation in reported incidence (Figure 3.3). Among these studies, annual incidence risk estimates for rickets or symptomatic vitamin D deficiency ranged from 2.2 to 7.5 per 100,000 children.

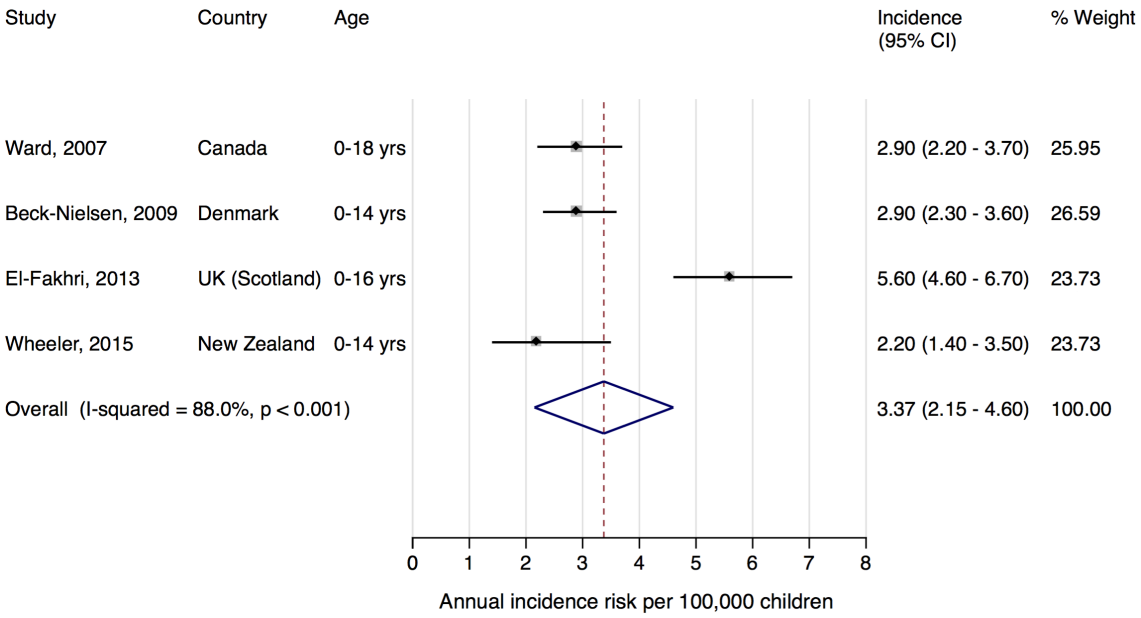
**Figure 3.3** Forest plot of incidence risk estimates for rickets or symptomatic vitamin D deficiency, restricted to studies of higher methodological quality.[a]




Abbreviations: CI, confidence interval; N/A, not available; yrs, years.
[a] Overall annual incidence risk estimates from studies considered to be of higher methodological quality (see section 3.4.4), grouped by country of origin. The study time period and age of included children is also displayed for each study. Incidence estimates are represented by circles where 95% confidence intervals are not available.

After exclusion of the study by Callaghan et al (2006), which did not provide a 95% confidence interval, the pooled annual incidence risk estimate across the remaining four higher quality studies was 3.37 per 100,000 children (95% CI: 2.15 to 4.60) (Figure 3.4). The meta-analysis indicated a high level of statistical heterogeneity between the studies' incidence estimates ($I^2$ = 88%).

**Figure 3.4** Forest plot of the incidence of rickets or symptomatic vitamin D deficiency, restricted to studies of higher methodological quality, with a pooled summary estimate.[a]




Abbreviations: CI, confidence interval; yrs, years.
[a] Analysis restricted to studies which provided a 95% confidence interval around the incidence estimate, and to studies considered to be of higher methodological quality (see section 3.4.4). A random-effects model was used to calculate the pooled incidence risk estimate.

#### *3.4.5.2 Studies Investigating Hypocalcaemic Seizures Secondary to Vitamin D Deficiency*

The single study which specifically investigated hypocalcaemic seizures secondary to vitamin D deficiency reported an overall incidence risk estimate of 0.35 per 100,000 children aged 0 to 15 years (95% CI: 0.28 to 0.43) (Basatemur & Sutcliffe, 2015). This study is described in full in chapter 4.

### *3.4.6 Differences in Incidence by Socio-Demographic Factors*

#### *3.4.6.1 Age*

Four studies, all considered to be of higher methodological quality, reported incidence risk estimates stratified by age group (Basatemur & Sutcliffe, 2015; Beck-Nielsen et al, 2009a; Ward et al, 2007; Wheeler et al, 2015). The incidence of rickets or symptomatic vitamin D deficiency was consistently reported to be significantly higher among young children aged ≤2 years compared to older children aged ≥3 years (Table 3.6). The incidence of hypocalcaemic seizures secondary to vitamin D deficiency was considerably higher among infants aged <1 year compared to older children.

**Table 3.6** Studies reporting age-stratified incidence estimates for symptomatic vitamin D deficiency.

| Study | Location | Age group | Annual incidence risk per 100,000 children (95% CI) |
|---|---|---|---|
| ***Study outcome - symptomatic vitamin D deficiency:*** | | | |
| Beck-Nielsen, 2009 | Southern Denmark | 0 – 2 years | 5.8 (4.0 – 8.3) |
| | | *0 – 14 years (overall)* | *2.9 (2.3 – 3.6)* |
| Ward, 2007 | Canada | 0 – 1 year | 9 (6 – 12) |
| | | 1 – 2 years | 12 (8 – 16) |
| | | 3 – 7 years | 0.3 (0.1 – 0.7) |
| Wheeler, 2015 | New Zealand | 0 – 2 years | 10.5 (6.7 – 16.6) |
| | | 3 – 14 years | 0.1 (0.02 – 1.0) |
| ***Study outcome - hypocalcaemic seizures secondary to vitamin D deficiency:*** | | | |
| Basatemur, 2015 | UK & Ireland | <1 year | 4.5 (3.6 – 5.6) |
| | | 1 – 2 years | 0.2 (0.08 – 0.4) |
| | | 3 – 10 years | *No cases reported* |
| | | 11 – 15 years | 0.06 (0.02 – 0.1) |

Abbreviations: CI, confidence interval.

### 3.4.6.2 Ethnicity

Four studies reported incidence estimates stratified by ethnicity, shown in Table 3.7 (Basatemur & Sutcliffe, 2015; Beck-Nielsen et al, 2009a; Callaghan et al, 2006; Thacher et al, 2013). All four studies were conducted among populations of majority white (Caucasian) ethnicity. Two studies reported stratified incidence estimates among children from minority ethnic groups, but not among children of white ethnicity (Beck-Nielsen et al, 2009a; Thacher et al, 2013). Across all four studies, incidence estimates for symptomatic vitamin D deficiency were considerably higher among children from minority ethnic groups (black, Asian, and Middle Eastern) when compared to white children or overall incidence estimates. However, confidence intervals around the incidence estimates were only available in two of the studies (Basatemur & Sutcliffe, 2015; Beck-Nielsen et al, 2009a), limiting the conclusions that can be drawn from the data.

**Table 3.7** Studies reporting incidence estimates for symptomatic vitamin D deficiency stratified by ethnicity.

| Study | Location | Outcome | Age | Ethnic origin | Annual incidence risk per 100,000 children (95% CI) |
|---|---|---|---|---|---|
| Beck-Nielsen, 2009 | Southern Denmark | Symptomatic vitamin D deficiency | 0 – 14 years | Middle East | 85 (53 – 129) |
| | | | | Africa | 59 (22 – 129) |
| | | | | Asia | 18 (2.2 – 66) |
| | | | | *Overall* | *2.9 (2.3 – 3.6)* |
| Callaghan, 2006 | West Midlands, UK | Symptomatic vitamin D deficiency | 0 – 4 years | White | 0.4 (N/A) |
| | | | | South Asian | 38 (N/A) |
| | | | | Black | 95 (N/A) |
| Basatemur, 2015 | UK & Ireland | Hypocalcaemic seizures | 0 – 15 years | White | 0.04 (0.02 – 0.09) |
| | | | | South Asian | 2.6 (1.9 – 3.4) |
| | | | | Black | 2.1 (1.3 – 3.2) |
| | | | | Mixed & other | 0.37 (0.12 –0.88) |
| **Study** | **Location** | **Outcome** | **Age** | **Ethnic origin** | **Incidence rate per 100,000 person-years (95% CI)** |
| Thacher, 2013 *(study period 2000-2009)* | Olmsted County, Minnesota, USA | Symptomatic vitamin D deficiency | 0 – 2 years | Black | 220 (N/A) |
| | | | | *Overall* | *24.1 (N/A)* |

Abbreviations: CI, confidence interval; N/A, not available.

#### *3.4.6.3 Sex*

One study reported incidence estimates stratified by sex (Basatemur & Sutcliffe, 2015), with the incidence of hypocalcaemic seizures secondary to vitamin D deficiency reported to be 4-fold higher in males (0.57 per 100,000 boys aged 0 to 15 years, 95% CI: 0.45 to 0.71) compared to females (0.13 per 100,000 girls aged 0 to 15 years, 95% CI: 0.07 to 0.20).

### *3.4.7 Temporal Trends in Incidence*

Three studies reported incidence estimates over separate time periods, shown in Table 3.8 (Millette et al, 2014; Moy et al, 2012; Thacher et al, 2013). Millette et al (2014) reported an increase in the annual incidence of rickets among children aged ≤6 years in Quebec from 3.0 per 100,000 children in 2004, to 7.2 per 100,000 children in 2009. However, these estimates were based on very small numbers of cases with widely overlapping confidence intervals, and incidence was reported from two distinct 1-year time periods as opposed to continuous time-trend data, preventing any conclusions being drawn about temporal trends in incidence.

Thacher et al (2013) reported an increase in the incidence of rickets among children aged ≤2 years in Olmsted County, Minnesota, USA from 1990-1999 (3.7 per 100,000 person years) to 2000-2009 (24.1 per 100,000 person years). However, caution must be taken in drawing conclusions about temporal trends from this data, as confidence intervals were not provided and would be expected to be wide given the small number of cases in each time period (2 in 1990-999, 14 in 2000-2009).

Moy et al (2012) reported a decrease in the incidence of symptomatic vitamin D deficiency among children aged ≤4 years in inner-city Birmingham, UK following a local public health initiative in 2005 to provide universal free of charge vitamin D supplements to pregnant and lactating women and children aged under 5 years. The annual incidence risk decreased from 120 per 100,000 children in 2005, to 49 per 100,000 children in 2009-2010. However, caution must be taken in drawing conclusions about temporal trends from this data, as confidence intervals were not provided and incidence was reported from two distinct 1-year time periods as opposed to continuous time-trend data.

**Table 3.8** Studies reporting incidence estimates for symptomatic vitamin D deficiency over separate time periods.

| Study | Location | Age | Time period | Annual incidence risk per 100,000 children (95% CI) |
|---|---|---|---|---|
| Millette, 2014 | Quebec, Canada | 0 – 6 years | 2004 | 3.0 (0.6 – 8.8) |
| | | | 2009 | 7.2 (2.7 – 15.7) |
| Moy, 2012 | Inner-city Birmingham, UK | 0 – 4 years | 2005 | 120 (N/A) |
| | | | 2009 – 2010 | 49 (N/A) |
| **Study** | **Location** | **Age** | **Time period** | **Incidence rate per 100,000 person-years (95% CI)** |
| Thacher, 2013 | Olmsted County, Minnesota, USA | 0 – 2 years | 1990 – 1999 | 3.7 (N/A) |
| | | | 2000 – 2009 | 24.1 (N/A) |

Abbreviations: CI, confidence interval; N/A, not available.

### *3.4.8 Sources of Heterogeneity*

There were considerable differences among the included studies with respect to various important clinical and methodological characteristics, such as: the age of included children, the ethnic composition of study populations, whether or not children with underlying chronic conditions that predispose to vitamin D deficiency were excluded, differences in the setting from which cases were identified (e.g. both outpatient and inpatient, or inpatient only), differences in case definitions for the outcome, and differences in methods of data collection (e.g. prospective surveillance study, or retrospective analysis of healthcare administrative database). The number of included studies was not sufficient for subgroup analysis or meta-regression to be undertaken to further investigate possible sources of heterogeneity.

## 3.5 Discussion

### *3.5.1 Summary of Results and Comparison with Existing Studies*

The systematic review identified 13 studies reporting data concerning the incidence of symptomatic vitamin D deficiency in children. The majority of the studies originated from Europe and North America, and data was scarce to non-existent from Asia, Africa, and South America. There was considerable heterogeneity among the included studies with respect to the study populations, clinical and methodological characteristics, and the assessed risk of bias. There was a wide variation in reported annual incidence estimates, ranging between 0.3 to 3,800 per 100,000 children.

Among the subset of studies considered to have a lower risk of bias, and which included all presentations of symptomatic vitamin D deficiency as the outcome, there was substantially less variation in annual incidence estimates, which ranged between 2.2 to 7.5 per 100,000 children. A summary estimate for the annual incidence of symptomatic vitamin D deficiency, derived from four studies considered to be of higher methodological quality, was 3.37 per 100,000 children (95% CI: 2.15 to 4.60). The studies included in the meta-analysis all originated from high-income countries with populations of predominantly Caucasian (white) ethnicity (Canada, Denmark, New Zealand, and Scotland), and were similar in respect to the age range of included children (between 0-14 to 0-18 years). However, the pooled incidence estimate should be interpreted with caution, given the high level of statistical heterogeneity observed ($I^2$ = 88%).

One study specifically investigated the incidence of hypocalcaemic seizures secondary to vitamin D deficiency in the UK and Ireland, reporting an annual incidence estimate of 0.35 per 100,000 children aged 0 to 15 years (95% CI: 0.28 to 0.43) (Basatemur & Sutcliffe, 2015). This study is described in full in chapter 4.

Few studies have examined differences in the incidence of symptomatic vitamin D deficiency by children's socio-demographic characteristics. Data from three studies suggests that the incidence of symptomatic vitamin D deficiency overall is considerably higher among younger children aged ≤2 years (annual incidence estimates between 5.8 to 12 per 100,000 children) compared to older children aged ≥3 years (annual incidence estimates between 0.1 to 0.3 per 100,000 children). The incidence of hypocalcaemic seizures secondary to vitamin D deficiency was >20-fold higher in infants under 1 year of age compared to older children. The limited data available

regarding ethnic differences in the incidence of symptomatic vitamin D deficiency suggests that it is considerably higher among children from black, Asian, and Middle Eastern ethnic groups when compared to white children or overall incidence estimates from predominantly Caucasian populations. No studies have examined differences in the overall incidence of symptomatic vitamin D deficiency in children by gender, however the incidence of hypocalcaemic seizures secondary to vitamin D deficiency was 4-fold higher in boys compared to girls in results from a single study. There is insufficient data to draw any conclusions regarding temporal trends in the incidence of symptomatic vitamin D deficiency in children over the last 25 years.

As far as it has been possible to identify, this is the first systematic review to specifically investigate the incidence of symptomatic vitamin D deficiency in children. Both systematic and narrative reviews have been published which broadly explore the epidemiology, aetiology and clinical presentation of nutritional rickets worldwide (Creo et al, 2017; Prentice, 2013; Thacher et al, 2006). In contrast to the systematic review described in the chapter, these reviews were not focused on disease incidence, but also included studies which reported disease prevalence, as well case series which did not provide any measures of disease frequency. Although a considerably larger number of studies were included in these reviews, their findings were summarised very briefly, and there was no critical appraisal or quality assessment of the included studies. These reviews included prevalence studies from regions of the world for which incidence data was scare or non-existent, such as Africa, Asia, and the Middle East. However, dietary calcium deficiency is an important cause of rickets in developing countries, and few studies from these regions included biochemical assessment to help distinguish the relative contribution of vitamin D deficiency and calcium deficiency in the aetiology of rickets.

### *3.5.2 Study Strengths and Limitations*

A comprehensive search of the published literature was undertaken using multiple bibliographic databases. However, a limitation of the search strategy was that unpublished material or ‘grey literature’ was not specifically sought. The reporting of the systematic review followed the MOOSE guidelines for meta-analysis of observational studies in epidemiology (Stroup et al, 2000). Included studies were critically appraised for indicators of methodological quality, and for assessment of the risk of bias. However, as no established or validated tool exists for the quality assessment of studies of disease incidence, the assessment criteria for study quality and risk of bias

were constructed in an ad hoc manner specifically for this study. A limitation of the review methodology was that study assessment and selection was undertaken by a single researcher, as opposed to independent double screening by at least two investigators as recommended by published guidelines (Liberati et al, 2009).

The methodological quality of included studies was variable, with seven of the thirteen included studies (54%) considered to have either a high risk of bias or poor generalisability to the national population. The considerable heterogeneity between studies limited the ability to synthesise results across settings. Factors contributing to this heterogeneity include the lack of accepted diagnostic criteria for the outcome, which resulted in wide variation in the case definitions used by different studies, and differences in the demographic characteristics of different study populations (e.g. in terms of age and ethnicity). The studies included in the systematic review originated almost entirely from high-income countries with predominantly Caucasian populations, restricting the relevance of the findings to similar settings. Few studies reported incidence estimates stratified by socio-demographic factors, limiting the ability to investigate differences in incidence by age, sex, and ethnicity. The number of included studies was not sufficient to perform subgroup analysis or meta-regression to further investigate possible sources of heterogeneity, or differences in incidence rates in relation to socio-demographic factors. There was also insufficient data available to draw any conclusions regarding temporal trends in incidence.

### *3.5.3 Conclusion*

Overall, symptomatic vitamin D deficiency is relatively uncommon among children from high-income countries with populations of predominantly Caucasian ethnicity. The more reliable annual incidence estimates available from such settings range between 2.2 to 7.5 per 100,000 children. The limited evidence available suggests that symptomatic vitamin D deficiency is considerably more frequent (by between 1 to 2 orders of magnitude) among younger children aged ≤2 years compared to older children aged ≥3 years, and among children from black, Asian, and Middle Eastern ethnic minority groups compared to children from white ethnic backgrounds. Although anecdotal reports and local case series have raised concerns that symptomatic vitamin D deficiency may have increased in frequency among children in high-income countries in recent decades, there is insufficient epidemiological data available to draw any conclusions regarding temporal trends in incidence over the last 25 years. There is a lack of data regarding the incidence of symptomatic vitamin D deficiency among

children from regions such as Africa, Asia, the Middle East, and South America. The implications of the work described in this chapter, with respect to public health and future research, are further discussed in the final chapter of the thesis.

## Chapter 4

# Hypocalcaemic Seizures Secondary to Vitamin D Deficiency in Children: A Prospective, Population-Based Surveillance Study in the United Kingdom and Ireland

## 4.1 Introduction

Over the last two decades, anecdotal reports have raised concerns that increasing numbers of children are presenting to healthcare services in the United Kingdom (UK) with clinical complications of vitamin D deficiency (Allgrove, 2004; Davies & Shaw, 2011; Shaw & Pal, 2002). However, existing studies investigating symptomatic vitamin D deficiency among children in the UK have either been single- or multi-centre case series, without denominator data available for the calculation of incidence, or regional studies with limited generalisability to the national population (see chapter 2.7.2). The systematic review described in chapter 3 identified that no previous studies have reported incidence estimates for any of the clinical complications of vitamin D deficiency at the national level in the UK. This chapter describes a prospective surveillance study undertaken across the UK and Ireland, using the British Paediatric Surveillance Unit (BPSU) reporting system, investigating the incidence of hypocalcaemic seizures secondary to vitamin D deficiency in children.

## 4.2 Background

### *4.2.1 The British Paediatric Surveillance Unit*

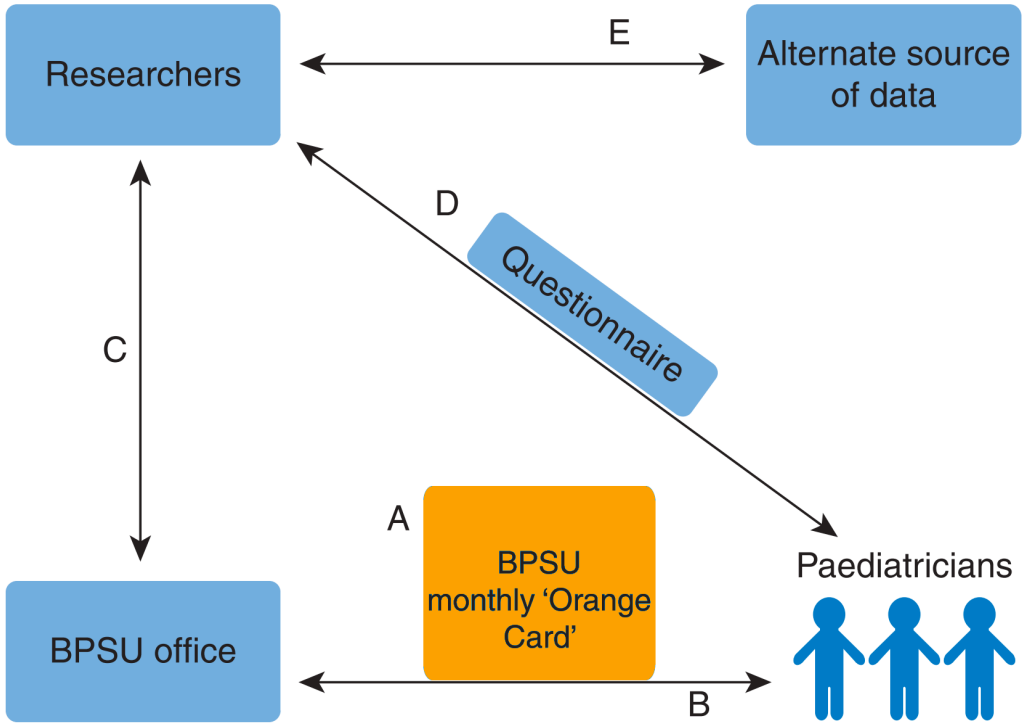
The British Paediatric Surveillance Unit (BPSU) was established in 1986, with the remit of facilitating research into rare childhood diseases. It has national coverage across the UK and Republic of Ireland, and uses an active method of surveillance with case reporting by consultant paediatricians and associate specialist paediatricians who have their own case load. In 2009, approximately 94% of all consultant paediatricians in the UK and Ireland participated in the BPSU reporting system (Knowles et al, 2012).

Each month all participating paediatricians are mailed or emailed a reporting card from the BPSU, known as the 'Orange Card'. The reporting card lists the conditions under surveillance, along with the reporting case criteria for each of the conditions. Recipients are asked to indicate the number of relevant cases that they have seen within the past month, or state that they have nothing to report, before returning the card to the BPSU. Follow-up reminders are sent to paediatricians who do not return their reporting cards. Response rates to BPSU reporting cards are high, with 95.3% of reporting cards returned in 2013 (BPSU, 2014). On receiving a case report, BPSU staff inform the

relevant study team, who send the reporting clinician a short data collection form to obtain case details. The BPSU methodology is summarised in Figure 4.1.

Researchers collect limited patient identifiable data in order to identify duplicate reports. However patient consent is not sought, as doing so would reduce case ascertainment and risk selection bias if certain groups of patients were more likely to refuse consent (Verity & Nicoll, 2002). Regulatory approval for the collection of patient identifiable data without consent, for research purposes, is obtained from the Confidentiality Advisory Group (CAG) at the NHS Health Research Authority, under section 251 of the NHS Act 2006. Prior to 2013, this responsibility of the CAG was undertaken by the National Information Governance Board for Health and Social Care (NIGB).

**Figure 4.1** The British Paediatric Surveillance Unit methodology.




Key: **A** The BPSU reporting card is sent to paediatricians every month. **B** Paediatricians return the reporting card to the BPSU office, to report the number of cases that they have seen in the preceding month, or to state that they have no cases to report. **C** BPSU staff inform researchers of paediatricians who have reported cases. **D** Researchers send reporting paediatricians a questionnaire to collect case details. **E** For some studies, cases may also be ascertained from alternative sources, for example laboratory surveillance systems, national death registration data, or surveillance systems involving reporting by other groups of specialist clinicians (Knowles et al, 2006). Figure adapted from Knowles et al. (2012).

### 4.2.2 Rationale for Investigating Hypocalcaemic Seizures Secondary to Vitamin D Deficiency Using the BPSU Methodology

In order to be appropriate for investigation using the BPSU reporting system, conditions must be relatively rare and should be principally managed by paediatricians (as opposed to being managed in primary care or by other specialties). At the time of the design of this study, the BPSU eligibility criteria stated that conditions 'should have an expected incidence in the UK of no more than 300 cases per year', so as not to exceed the unit's administrative capacity (Knowles et al, 2010).

It was considered that symptomatic vitamin D deficiency in its entirety may not to be suitable for investigation using the BPSU methodology, for two reasons. Firstly, it was predicted that the incidence may exceed 300 cases per year in children in the UK and Ireland. The incidence of symptomatic vitamin D deficiency in children aged 0 to 4 years in the West Midlands had previously been estimated at 7.5 per 100,000 children per year (Callaghan et al, 2006). Based on mid-2010 population estimates of 4.22 million children aged between 0 to 4 years in the UK and Republic of Ireland (CSO, 2014; ONS, 2013c), an incidence rate of 7.5 per 100,000 would equate to an estimated 316 cases per year nationally in this age group alone. Although one would expect incidence rates for symptomatic vitamin D deficiency to be lower nationally than in the West Midlands, due to the large South Asian population resident in this region, further cases would be expected among older children aged 5 years and above.

Secondly, health professionals who do not participate in BPSU surveillance may manage certain presentations of vitamin D deficiency. Less severe presentations of rickets or osteomalacia with non-specific musculoskeletal pain or muscle weakness, particularly in older children, may be managed in primary care. Children with skeletal deformities secondary to rickets may be referred to orthopaedic surgeons rather than paediatricians (Naseem et al, 2011). This could result in under-ascertainment of cases with musculoskeletal manifestations of vitamin D deficiency.

However, the BPSU reporting system was considered to be suitable for investigation of the most common acute presentation of vitamin D deficiency: hypocalcaemic seizures (see chapter 2.3.2 and 2.7.2). In the UK, the care of children with hypocalcaemic seizures is likely to be managed almost exclusively by paediatricians. The incidence of hypocalcaemic seizures secondary to vitamin D deficiency was predicted not to exceed the recommended capacity of BPSU studies. In Callaghan and colleagues (2006) survey of West Midlands paediatricians, 6 out of the reported 25 cases (25%)

presented with hypocalcaemic seizures, equating to an estimated annual incidence of 1.88 per 100,000 children age between 0 to 4 years. Using mid-2010 population estimates (CSO, 2014; ONS, 2013c), this gives an estimate of 79 cases per year in the UK and Ireland in this age group. A relatively small number of additional cases would be expected in older children; previous case series have reported that the majority (76% to 85%) of children with hypocalcaemic presentations of vitamin D deficiency are less than 3 years of age (Ladhani et al, 2004; Robinson et al, 2006).

## 4.3 Aims and Objectives

### *4.3.1 Study Aims*

The overall aim of this study was to describe the epidemiology in the UK of one of the acute clinical presentations of vitamin D deficiency in children, hypocalcaemic seizures.

### *4.3.2 Study Objectives*

i) To estimate the overall incidence of hypocalcaemic seizures secondary to vitamin D deficiency in children in the UK and Ireland, and the incidence stratified by sex, age and ethnicity.

ii) To describe the demographic and clinical characteristics of affected children.

iii) To summarise the biochemical profile, and other investigation results, in affected children.

iv) To describe the clinical management of affected children.

v) To determine the clinical outcomes in affected children.

## 4.4 Methods

### *4.4.1 Study Design*

This was a prospective national surveillance study, using the British Paediatric Surveillance Unit reporting system (see section 4.2.1).

### *4.4.2 Study Surveillance Period*

Surveillance of hypocalcaemic seizures secondary to vitamin D deficiency was conducted for a 2-year period, between September 2011 and September 2013, during which the condition was listed on the monthly BPSU reporting card (the 'Orange Card').

### *4.4.3 Correspondence with Reporting Clinicians*

The study team was informed of all case notifications for the study by BPSU staff on a weekly basis, and provided with contact details for the paediatricians who reported the cases. Reporting clinicians were subsequently contacted by both post and email, with a cover letter (see appendix D.1) thanking them for reporting the case and politely requesting them to complete an attached data collection form (see appendix D.2), in order to confirm case status and obtain demographic and clinical details regarding the case. A reminder letter and email was sent to paediatricians who did not return the data collection form within three to four weeks of the initial request. If reporting clinicians did not respond within a further three weeks of the reminder letter, they were contacted by telephone (a minimum of three attempts on separate days).

### *4.4.4 Case Definition*

A surveillance case definition was used to provide case reporting criteria for paediatricians, and a narrower analytic case definition was used to subsequently confirm case status. Separate surveillance and analytic case definitions were used to simplify the reporting criteria, and thus minimise any under-reporting of cases arising from uncertainty or complexity regarding the reporting criteria. The surveillance case

definition, which was included on the monthly BPSU reporting card, is shown in Box 4.1:

**Box 4.1** Surveillance case definition.

Any child under 16 years of age who develops a suspected seizure* in the presence of BOTH of the following biochemical criteria:

1. Low serum corrected calcium: <2.0 mmol/l
2. Low serum 25-hydroxyvitamin D level: <50 nmol/l (<20 ng/ml)

Excluding children with a history of a previous confirmed hypocalcaemic seizure due to vitamin D deficiency (prior to this presentation).

*Include cases where the event is felt to most likely represent a true seizure, as opposed to another paroxysmal event. A seizure can be defined as a paroxysmal, time-limited change in motor activity and/or behaviour that results from abnormal electrical activity in the brain.

The 25-hydroxyvitamin D (25-OH-D) cut-off of 50 nmol/l represents the level below which vitamin D status is defined as 'insufficient' in UK paediatric guidelines, although the evidence base underpinning 25-OH-D thresholds is limited (see chapter 2.4) (Arundel et al, 2012; Arundel & Shaw, 2015; RCPCH, 2013). Severe manifestations of vitamin D deficiency, such a frank rickets and hypocalcaemic symptoms, are generally thought to occur with 25-OH-D levels below 25 nmol/l, which is defined as 'deficiency' in UK guidance (Pearce & Cheetham, 2010; Shaw & Mughal, 2013a). However, a number of case series have reported that children with symptomatic vitamin D deficiency, including those with hypocalcaemic presentations, can have 25-OH-D levels in the 'insufficient' range of 25-50 nmol/l (Ahmed et al, 2011; Sharma et al, 2009; Wheeler et al, 2015). Therefore, the cut-off of <50 nmol/l was chosen for the study case definition, as opposed to <25 nmol/l, in order to minimise the risk of case under-ascertainment.

The analytic case definition was identical to the surveillance case definition, with the addition of the following exclusion criteria:

i) Presence of an alternative cause of seizures (other than hypocalcaemia) at the time of the event.

ii) Presence of an underlying pathology that can cause secondary vitamin D deficiency, by interfering with vitamin D absorption or metabolism.

Information regarding the above exclusion criteria was obtained using the data collection form (see appendix D.2). The presence or absence of the following conditions that can cause seizures was specifically sought in the data collection form; central nervous system infection (meningitis or encephalitis), central nervous system ischaemic or haemorrhagic events (intracranial haemorrhage, cerebral infarction, or hypoxic ischaemic encephalopathy), hypoglycaemia, severe hypernatraemia (>155 nmol/l) or hyponatraemia (<125 nmol/l), epilepsy, drug withdrawal, and inborn errors of metabolism. The presence or absence of the following conditions that can cause secondary vitamin D deficiency was specifically sought in the data collection form; chronic renal disease, liver disease, gastrointestinal disease with malabsorption, conditions necessitating total parenteral nutrition, and inherited disorders of vitamin D metabolism.

Cases that met the analytic case definition were defined as ‘confirmed’ cases. During data collection, a number of cases were reported in which serum 25-OH-D measurements were unavailable, because blood samples taken at presentation were insufficient for analysis. However, the working diagnosis in all of these cases was that of a hypocalcaemic seizure secondary to vitamin D deficiency. Excluding these cases would have resulted in case under-ascertainment. Therefore, such cases were defined as ‘probable’ cases if they otherwise met the analytic case definition, and if one or more of the following additional features suggestive of metabolic bone disease secondary to vitamin D deficiency were present:

i) High serum alkaline phosphatase (ALP), according to local laboratory reference range.

ii) High serum parathyroid hormone (PTH), according to local laboratory reference range.

iii) Radiological features suggestive of rickets, as reported by the clinician.

### 4.4.5 Data Collection Form

The data collection form was designed to take no longer than 10 to 15 minutes to complete, so as not to impose an excessive burden on reporting clinicians. Participation in the BPSU reporting system is voluntary, and paediatricians who report cases do not receive any incentive for doing so. Requesting clinicians to complete a longer or more time consuming questionnaire would risk compromising return rates.

The data collection form was designed to only request information that was likely to be readily available in the clinical case notes, i.e. information that would be documented as part of routine clinical care. Paediatricians would generally be expected to complete the questionnaire some time, typically weeks to months, after the child had presented. Therefore, they were not expected to have access to the child or their family to clarify specific study questions.

Feedback on the design and content of the data collection form was requested from a convenience sample of 14 consultant paediatricians, of whom 8 responded. Their comments were incorporated into the final questionnaire design.

The data collection form requested details regarding the demographics, clinical presentation, co-morbidities, investigation results, and clinical management of cases. See appendix D.2 for a copy of the data collection form. Information regarding ethnicity was collected using the UK Census 2001 categories (ONS, 2001). Gestational age was categorised using the World Health Organisation definitions of prematurity (Blencowe et al, 2012). The following patient identifiable data was collected in order to identify duplicate reports; NHS number, local hospital number, date of birth, sex, and district level partial postcode.

### 4.4.6 Population Estimates

Population estimates from the Office for National Statistics (ONS) for the UK, and the Central Statistics Office (CSO) for the Republic of Ireland, were used to estimate the population at risk for the calculation of incidence. For the calculation of overall incidence, and incidence stratified by age and sex, mid-2012 population estimates from the ONS (2013b) and 2012 population estimates from the CSO (2014) were used, as this represents the study midpoint. Population data stratified by ethnicity was only available for children aged between 0 to 14 years in England, Wales, and Republic of

Ireland, using 2011 census population estimates (CSO, 2012; ONS, 2013a). Population estimates stratified by ethnicity were not available for Scotland or Northern Ireland.

### *4.4.7 Statistical Analysis*

Analyses were primarily descriptive. Data were summarised using means and standard deviations (SD) for approximately normally distributed data, and using medians and interquartile ranges (IQR) for non-normally distributed data. Annual incidence estimates were calculated as follows:

number of cases during the study period ÷ (population at risk x 2)

95% confidence intervals (CI) around incidence estimates were calculated using the exact Poisson method. Differences in biochemical test parameters by age and sex were examined using independent t-tests for normally distributed data, and Wilcoxon rank sum tests for non-normally distributed data. Analyses were performed using Stata SE version 13.1 (StataCorp, USA).

### *4.4.8 Ethical Approval*

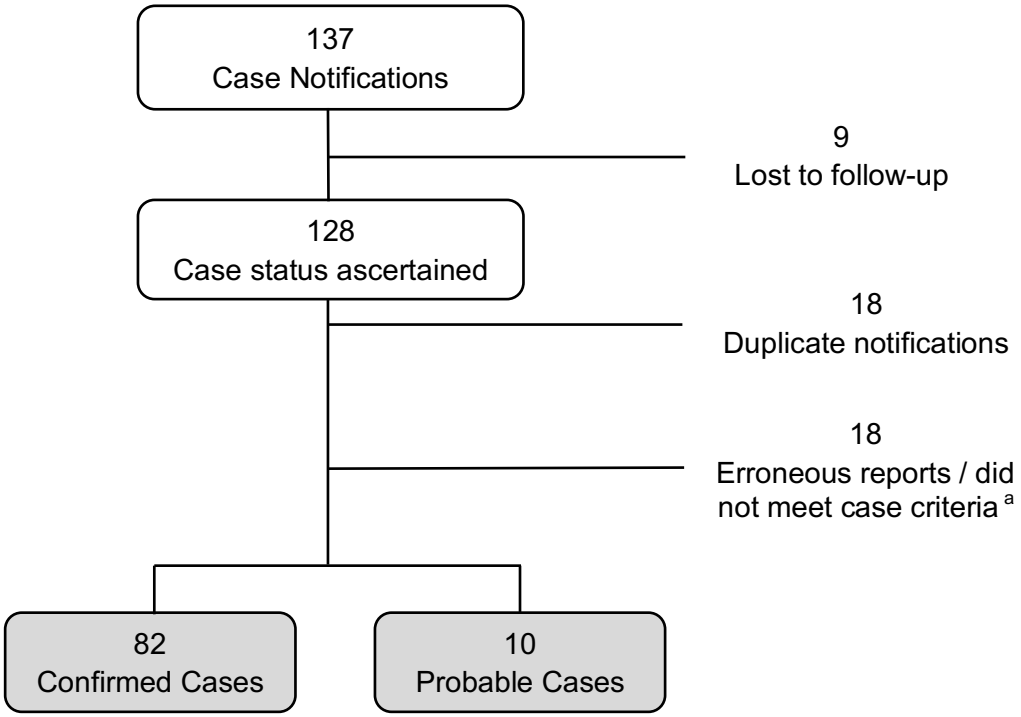
Ethical approval for the study was obtained from the London Central Research Ethics Committee (reference 11/LO/0838, see appendix B.1). Approval for the collection of patient identifiable data without consent was obtained from the Ethics and Confidentiality Committee of the National Information Governance Board for Health and Social Care (NIGB), under Section 251 of the NHS Act 2006 (reference ECC/ BPSU/6-02(FT7)/2011, see appendix B.2). Following a two-stage scientific review process, the study was approved for inclusion in the BPSU reporting system by the BPSU Executive Committee (see appendix B.3).

## 4.5 Results

### *4.5.1 Status of Reported Cases*

There were 137 case notifications in total during the study period, of which 82 were confirmed cases and 10 were probable cases (Figure 4.2).[1] There were 18 duplicate notifications, and 18 cases were reported in error or did not meet the case criteria. It was not possible to ascertain case status for 9 notifications (7%), either because the reporting consultants were unable to recall the patient's identifiers and locate the case notes (n=6), or because they were not contactable or did not return the data collection form despite several reminders (n=3). The 92 confirmed and probable cases were included for the subsequent analyses.

**Figure 4.2** Flow diagram of case notifications.




[a] 7 cases occurred prior to the study surveillance period, 3 had tetany rather than seizures, 2 did not have a serum 25-OH-D available and did not meet the criteria for a probable case, 1 was age 17 years at the time of the seizure, 1 had a previous hypocalcaemic seizure due to vitamin D deficiency, 1 was an overseas patient not resident in the UK, and 1 child was known to have velocardiofacial syndrome and hypoparathyroidism which was an alternative explanation for the hypocalcaemia. In 2 cases, the paediatrician did not intend to report a case for the study (the notification was in error).

[1] The data collection form for one case was returned by the clinician 2 years after the initial case report, following publication of the results of the study in *The Journal of Clinical Endocrinology and Metabolism* (see appendix A.1). Therefore, the number of confirmed cases included in the analyses reported in the published paper is one less (81) than described in this thesis.

### 4.5.2 Demographic Characteristics

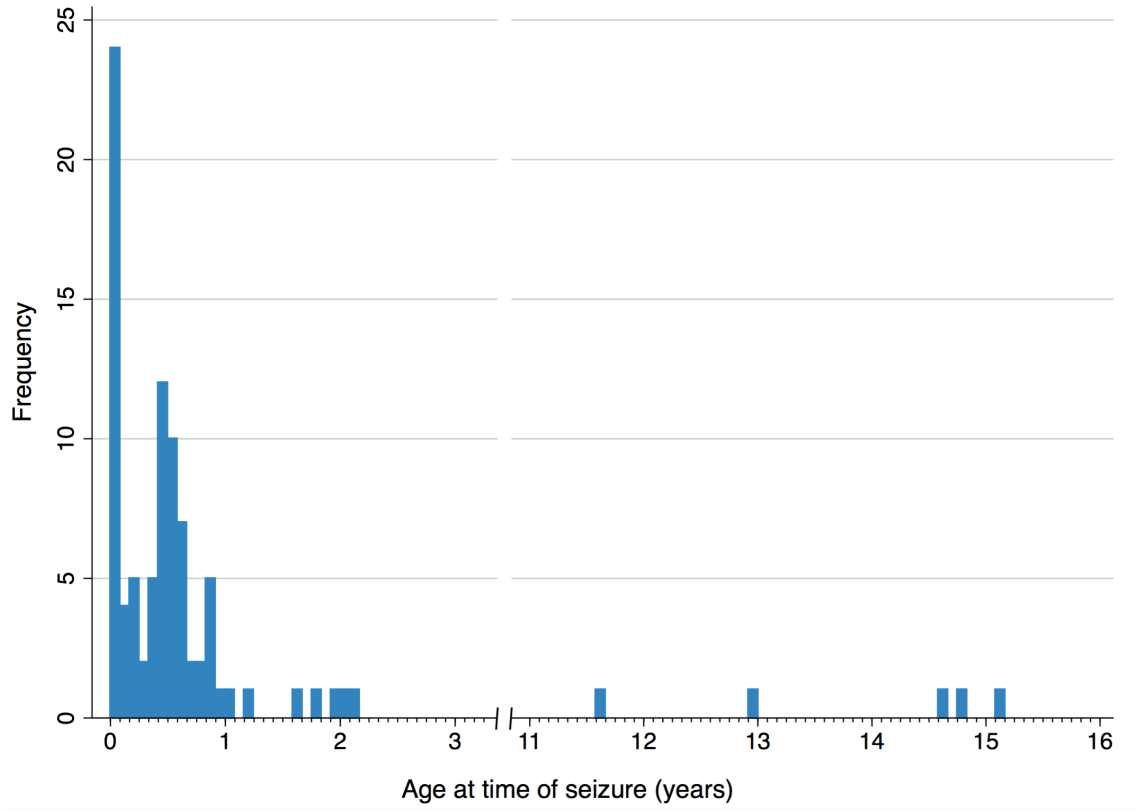
Demographic characteristics of the included cases are shown in Table 4.1. There was a marked difference in the number of cases by sex, with 83% being male. Cases fell into two distinct age groups; 95% of cases were young children aged between 0 and 2 years (n=87), and the remaining 5% (n=5) were adolescents aged between 11 and 15 years (Figure 4.3). The majority of cases were infants less than 1 year of age (87%), and a significant proportion of cases were neonates below 1 month of age (26%).

**Table 4.1** Demographic characteristics of cases.

| **Country** (n=92) | **n (%)** |
|---|---|
| England | 83 (90%) |
| Scotland | 3 (3%) |
| Wales | 1 (1%) |
| Northern Ireland | 2 (2%) |
| Republic of Ireland | 3 (3%) |
| **Sex** (n=92) | **n (%)** |
| Male | 76 (83%) |
| Female | 16 (17%) |
| **Ethnicity** (n=92) | **n (%)** |
| Any white background | 11 (12%) |
| Pakistani | 35 (38%) |
| Indian | 11 (12%) |
| Other South Asian[a] | 8 (9%) |
| Black (African / Caribbean / other) | 22 (24%) |
| Mixed & other ethnicity[b] | 5 (5%) |
| **Age in months at presentation** (n=92) | **Median (IQR)** |
| | 5.5 (0.9–8.0) |
| **Gestation at birth** (n=84) | **n (%)** |
| ≥ 37 weeks | 77 (92%) |
| 32 – 36 weeks | 6 (7%) |
| < 28 weeks | 1 (1%) |

Abbreviations: IQR, interquartile range.
[a] 3 Bangladeshi, 2 Afghan, 3 unspecified Asian background.
[b] 2 children with mixed ethnicity, 1 Libyan, 1 Iranian, and 1 Iraqi.

**Figure 4.3** Distribution of cases by age.

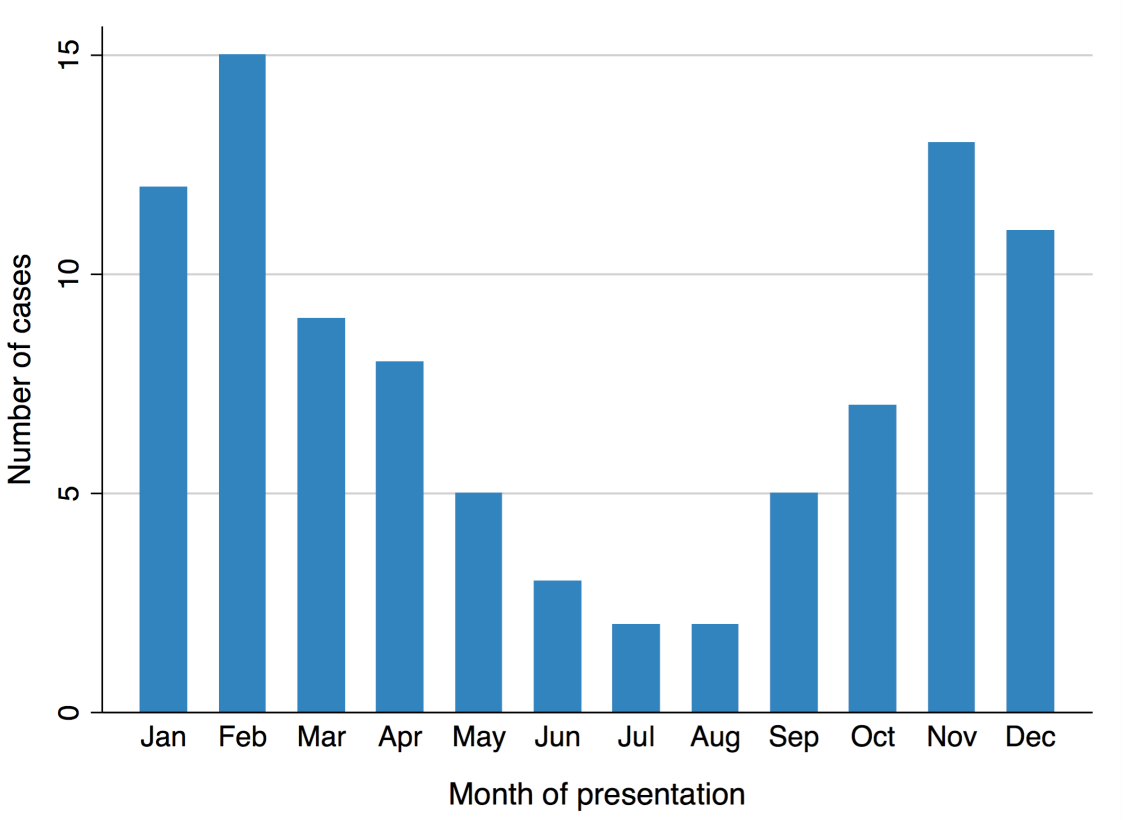



The majority of cases were from ethnic groups known to be at high risk of vitamin D deficiency; 59% (n=54) were of South Asian ethnicity and 24% (n=22) were black. 12% (n=11) came from a white background. Data regarding gestational age at birth was missing for 8 cases (9%). Among cases with data available for gestational age, the majority (92%) were born at term (≥37 weeks gestation). 6 children (7%) were moderate to late preterm (32 to 36 weeks gestation), and one case (1%) was extremely preterm (<28 weeks).

### *4.5.3 Seasonal Variation in Presentation*

There was a marked seasonal pattern in presentation, with 74% of cases occurring between November to April (Figure 4.4).

**Figure 4.4** Distribution of cases by calendar month.




### *4.5.4 Incidence Estimates*

The estimated annual incidence of hypocalcaemic seizures secondary to vitamin D deficiency was 3.53 per million children aged 0 to 15 years (95% CI: 2.84 to 4.33). Incidence was significantly greater in males compared to females, in infants compared to older children, and in children of South Asian or black ethnicity compared to children from white ethnic backgrounds (Table 4.2).

Population estimates stratified by ethnicity are not available by single year of age. However, approximate population estimates for infants (under 1 year of age) stratified by ethnicity can be derived for England, Wales and Republic of Ireland by applying the ethnicity distribution for children aged 0 to 4 years in the 2011 census (CSO, 2012; ONS, 2013a) to overall population estimates for infants in 2012 (CSO, 2014; ONS, 2013b). This gives estimated incidence of 30.9 per 100,000 South Asian infants (95% CI: 22.6 to 41.2), 26.9 per 100,000 black infants (95% CI: 16.7 to 41.2), and 0.32 per 100,000 white infants (95% CI: 0.09 to 0.81).

**Table 4.2** Annual incidence estimates: overall and stratified by sex, age, and ethnicity.

| | Number of cases [a] | Population estimate | Annual incidence per million (95% CI) |
|---|---|---|---|
| **All children age <16 years** | 92 | 13,037,071 [b] | 3.53 (2.84–4.33) |
| **Stratified by sex** | | | |
| Male | 76 | 6,673,852 [b] | 5.69 (4.49–7.13) |
| Female | 16 | 6,363,219 [b] | 1.26 (0.72–2.04) |
| **Stratified by age** | | | |
| < 1 year | 80 | 890,510 [b] | 44.9 (35.6–55.9) |
| 1 – 2 years | 7 | 1,745,821 [b] | 2.00 (0.81–4.13) |
| 3 – 10 years | 0 | 6,430,876 [b] | - |
| 11 – 15 years | 5 | 3,969,864 [b] | 0.63 (0.20–1.47) |
| **Stratified by ethnicity** [c] | | | |
| White | 8 | 8,674,415 [d] | 0.46 (0.20–0.91) |
| South Asian | 52 | 998,463 [d] | 26.0 (19.4–34.1) |
| Black | 21 | 507,205 [d] | 20.7 (12.8–31.6) |
| Mixed & other | 5 | 662,816 [d] | 3.77 (1.22–8.80) |

[a] Number of confirmed and probable cases over the 2-year study period
[b] Mid-2012 population estimates for children aged 0 to 15 years in England, Wales, Scotland, Northern Ireland, & Republic of Ireland.
[c] Analysis stratified by ethnicity only includes children aged 0 to 14 years in England, Wales & Republic of Ireland (n=86), as population estimates by ethnicity are not available for children in Scotland and Northern Ireland, or for children aged 15 years in the Republic of Ireland.
[d] Mid-2011 population estimates for children aged 0 to 14 years in England, Wales, & Republic of Ireland.

### *4.5.5 Risk Factors for Vitamin D Deficiency*

Information regarding type of feeding was available for 98% of children under 1 year of age (Table 4.3). Although most cases were exclusively breastfed (55%), 15 (19%) were exclusively formula milk fed. 14 of these 15 (93%) were neonates under one month of age. Information regarding whether or not the mother was veiled / covered was available for 77% of cases. Of these, 46% of mothers were reported to have some degree of veiling / covering (either full length or a head scarf). There was a substantial proportion of missing data regarding maternal use of vitamin D supplements during pregnancy (38% missing) and breastfeeding (26% missing). Among cases age <2 years, 8% (n=4) of mothers were reported to have taken vitamin D supplements during pregnancy. Information regarding the preparation of vitamin D was available for 2 of these cases (Adcal D3 in one, non-specified multivitamin in the other), however the

dose was not available for either case. Among cases who were breastfed, 6% of mothers were reported to be taking vitamin D supplements at the time of presentation. Information regarding the preparation and dose of vitamin D was not available in any of these cases.

**Table 4.3** Risk factors for vitamin D deficiency among cases.

| | n (%) |
|---|---|
| **Diet if age <1 year** (n=78) [a] | |
| Exclusively breast fed | 43 (55%) |
| Formula milk | 15 (19%) |
| Mixed breast milk & formula | 7 (9%) |
| Weaned onto solids | 13 (17%) |
| **Mother veiled / covered** (n=71) | |
| Yes | 33 (46%) |
| No | 38 (54%) |
| **If child aged <2 years, did the mother take vitamin D supplements during pregnancy** (n=53) [b] | |
| Yes | 4 (8%) |
| No | 49 (92%) |
| **If child breastfed, was mother taking vitamin D supplements** (n=52) [c] | |
| Yes | 3 (6%) |
| No | 49 (94%) |

[a] Total number of cases aged <1 year = 80. Data missing for 2 cases. All children age ≥1 year were weaned onto solids.
[b] Total number of cases aged <2 years = 85. Data missing for 32 cases.
[c] 22 cases reported as not breastfeeding. Number of cases with data missing = 18.

### *4.5.6 Clinical Characteristics*

61% of cases had multiple seizures (Table 4.4). In the majority of children, seizure duration was less than 5 minutes (60%), with more prolonged seizures lasting ≥10 minutes in 20% of cases. 80% of children did not have any other clinical features of vitamin D deficiency, whilst 15% exhibited features of rickets.

**Table 4.4** Clinical characteristics of cases.

| **Number of seizures** (n=92) | **n (%)** |
|---|---|
| 1 | 36 (39%) |
| 2 – 5 | 37 (40%) |
| > 5 | 19 (21%) |
| **Duration of longest seizure in minutes** (n=85) | **Median (IQR)** |
| | 3 (2–7) |
| **Other clinical manifestations of vitamin D deficiency** (n=92) | **n (%)** |
| None | 74 (80%) |
| Rickets [a] | 14 (15%) |
| Stunted growth | 4 (4%) |
| Fracture | 1 (1%) |
| Muscular cramps & paraesthesia | 1 (1%) |

Abbreviations: IQR, interquartile range.
[a] Skeletal features reported included bowed legs, joint swelling, ricketary rosary, and craniotabes.

### *4.5.7 Investigations*

Serum biochemistry results are shown in Table 4.5. Where available, serum 25-OH-D levels were <25 nmol/l in 87% of children, and between 25-50 nmol/l in 13%. Median ALP and PTH levels were above normal, whilst the mean phosphate was at the upper end of the normal range. Exploration of the relationship between age and serum biochemistry using scatterplots suggested that neonates (age <1 month) exhibited lower ALP and PTH levels, and higher phosphate levels, than older children (Figure 4.5). These differences were statistically significant (Table 4.6). There were no significant differences in serum biochemistry between males and females, although the analysis is limited by small numbers of females resulting in wide confidence intervals in this group (Table 4.7). Where the maternal 25-OH-D level was available (48% of cases), it was <25 nmol/l in 72% and between 25-50 nmol/l in 26% of cases. Radiographs were performed in 30 cases (33%), of which 23 were reported to have features of rickets present (77%). Electrocardiograms were performed in 40 cases (43%), of which 16 were reported to have a prolonged QT interval (40%).

**Table 4.5** Investigation results.

| **Serum biochemistry** [a] | **Median (IQR)** |
|---|---|
| 25-hydroxyvitamin D (nmol/l) (n=82) | 11.1 (8.0–19.2) |
| Alkaline phosphatase (iu/l) (n=90) | 683 (452–1,003) |
| Parathyroid hormone (pmol/l) (n=73) | 21.3 (9.0–36.6) |
| | **Mean (SD)** |
| Corrected calcium (mmol/l) (n=92) | 1.42 (0.21) |
| Phosphate (mmol/l) (n=87) | 2.13 (0.75) |
| **Maternal 25-OH-D (nmol/l)** (n=43) | **Median (IQR)** |
| | 18.5 (12.0–27.9) |
| **X-ray of a long bone** (n=30) | **n (%)** |
| Signs of rickets present | 23 (77%) |
| **Electrocardiogram** (n=40) | **n (%)** |
| Prolonged QT interval present | 16 (40%) |

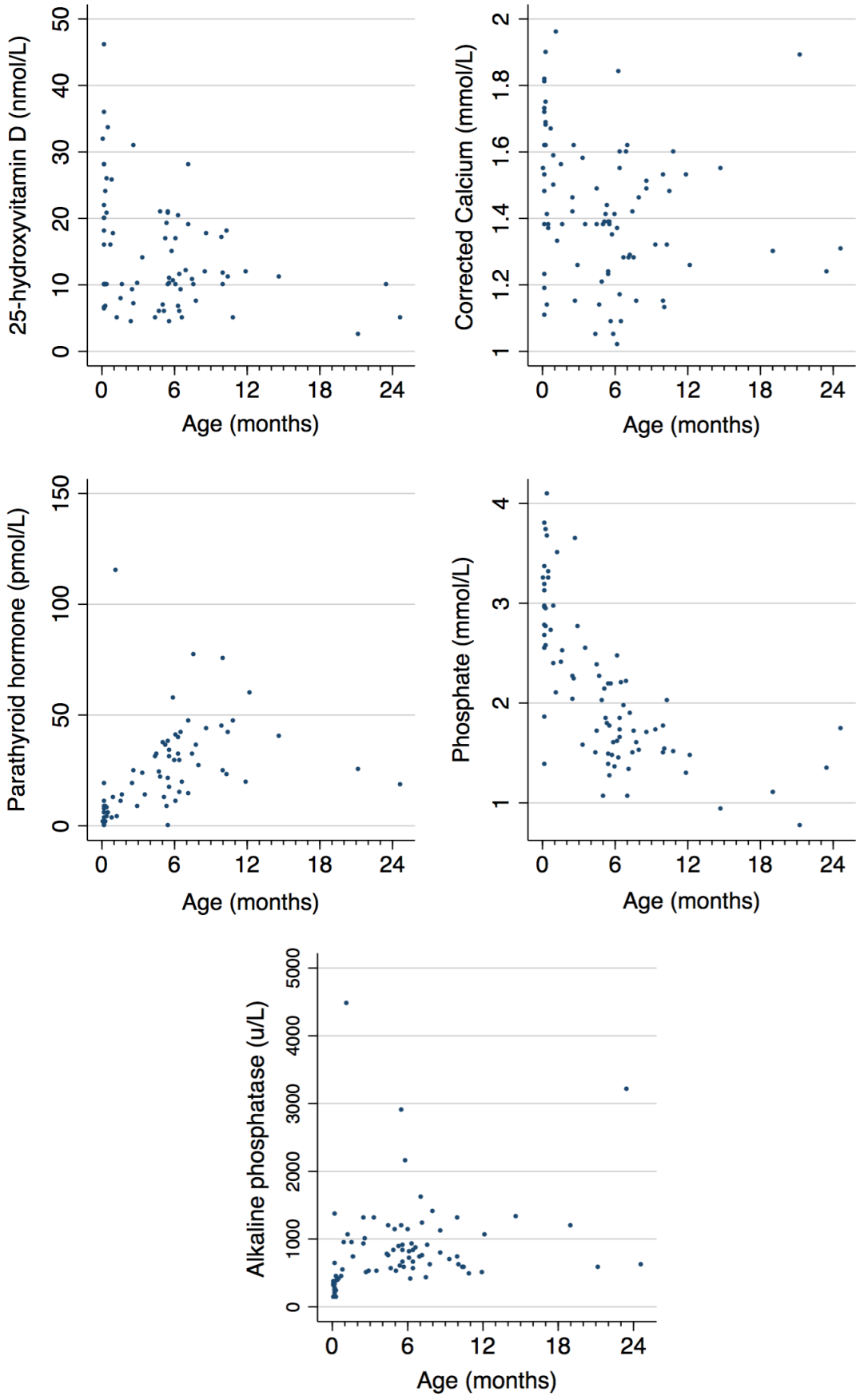
Abbreviations: 25-OH-D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; IQR, interquartile range; PTH, parathyroid hormone; SD, standard deviation.
[a] Reference ranges vary by lab. Indicative reference values from University College London Hospital are as follows. ALP: upper limit of normal varies with age, between 250-460 iu/l. PTH: 1.6-6.9 pmol/l. Calcium: 2.15-2.55 mmol/l. Phosphate: age 10d to 2yr = 1.45-2.16 mmol/l, age 2yr to 13yr = 1.45-1.78 mmol/l.

**Table 4.6** Differences in serum biochemistry between neonates and older children.

| **Test** (units) (n) | **Age <1 month** | **Age >1 month** | |
|---|---|---|---|
| | Median (95% CI) | Median (95% CI) | p-value [a] |
| 25-OH-D (nmol/l) (n=82) | 20.1 (13.9–25.9) | 10.3 (10–11.6) | <0.001 |
| ALP (iu/l) (n=90) | 351 (256–406) | 820 (725–928) | <0.001 |
| PTH (pmol/l) (n=73) | 5.9 (2.8–8.6) | 27.4 (21.8–33.1) | <0.001 |
| | Mean (95% CI) | Mean (95% CI) | p-value [b] |
| Co. $Ca^{2+}$ (mmol/l) (n=92) | 1.54 (1.44–1.63) | 1.38 (1.33–1.43) | 0.002 |
| Phosphate (mmol/l) (n=87) | 2.97 (2.71–3.24) | 1.83 (1.70–1.97) | <0.001 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; CI, confidence interval; Co. $Ca^{2+}$, corrected calcium; PTH, parathyroid hormone; SD, standard deviation.
[a] p-value for no difference using Wilcoxon rank sum test.
[b] p-value for no difference using independent t-test.

**Figure 4.5** Scatterplots of serum biochemistry by age.[a]




[a] Graphs limited to cases age 0-2 years, for purposes of clarity.

**Table 4.7** Differences in serum biochemistry by sex.

| **Test** (units) (n) | **Male** | **Female** | |
|---|---|---|---|
| | Median (95% CI) | Median (95% CI) | p-value [a] |
| 25-OH-D (nmol/l) (n=82) | 11.1 (10.0–14.6) | 14.2 (9.1–28.5) | 0.15 |
| ALP (iu/l) (n=90) | 718 (585–820) | 529 (246–1,097) | 0.34 |
| PTH (pmol/l) (n=73) | 21.3 (14.7–26.7) | 27.7 (2.9–42.1) | 0.82 |
| | Mean (95% CI) | Mean (95% CI) | p-value [b] |
| Co. $Ca^{2+}$ (mmol/l) (n=92) | 1.43 (1.38–1.47) | 1.39 (1.25–1.53) | 0.55 |
| Phosphate (mmol/l) (n=87) | 2.10 (1.93–2.67) | 2.30 (1.76–2.84) | 0.37 |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; CI, confidence interval; Co. $Ca^{2+}$, corrected calcium; PTH, parathyroid hormone; SD, standard deviation.
[a] p-value for no difference using Wilcoxon rank sum test.
[b] p-value for no difference using independent t-test.

### *4.5.8 Clinical Management and Outcomes*

97% of cases were admitted to hospital, for a median duration of 3 days (IQR: 2 – 5). Approximately half of the children (51%) were given acute treatment in order to terminate a seizure or prevent seizure recurrence; 44% received intravenous calcium gluconate, and 27% received anticonvulsant medication (Table 4.8). 79 children (87%) were given vitamin D replacement as either colecalciferol or ergocalciferol, with 10 (11%) given single high-dose (stoss) therapy (administered intramuscularly in 8 cases and orally in 2 cases). 12 children (13%) received alfacalcidol, whilst 3 children (3%) were reported to have received vitamin D replacement only in the form of Abidec or Dalivit multivitamin preparations.

Among children who received colecalciferol or ergocalciferol, information regarding the dose prescribed was available for 71% of cases. The dose prescribed was in accordance with the dosage recommendations by age from the British National Formulary for Children (BNFc) in 69% of cases (BNFc, 2014). A lower dose than that recommended in the BNFc was prescribed in 23%, and a higher dose in 8%.

None of the children died. One case had sequelae at the time of discharge (a burn from extravasation of intravenous calcium gluconate).

**Table 4.8** Clinical management.

| | | n (%) |
|---|---|---|
| **Acute treatment to terminate / prevent seizures** (n=90) | | |
| None | | 44 (49%) |
| Intravenous calcium gluconate | | 40 (44%) |
| Anticonvulsant: | Any | 24 (27%) |
| | Benzodiazepine | 13 (14%) |
| | Phenobarbitone | 11 (12%) |
| | Phenytoin | 5 (6%) |
| **Vitamin D replacement therapy** (n=91) | | |
| Colecalciferol or ergocalciferol | | 79 (87%) |
| Alfacalcidol | | 12 (13%) |
| Multivitamin preparation (Abidec or Dalivit) | | 11 (12%) |
| Adcal D3 | | 2 (2%) |

## 4.6 Discussion

### *4.6.1 Summary of Results and Comparison with Existing Studies*

This chapter describes the first study in the UK to report national incidence estimates for any of the clinical manifestations of vitamin D deficiency. There were 92 confirmed and probable cases of hypocalcaemic seizures secondary to vitamin D deficiency during the 2-year study period, equating to an overall annual incidence of 3.53 per million children aged 0 to 15 years (95% CI: 2.84 to 4.33). As described in chapter 2.7.2, most previous studies of symptomatic vitamin D deficiency in children in the UK have been single or multi-centre case series, with the exception of two regional prospective studies (Callaghan et al, 2006; El-Fakhri et al, 2013). Although based on small numbers of cases, incidence estimates for hypocalcaemic seizures due to vitamin D deficiency can be derived from the results of these studies, and are broadly similar to the national incidence estimates described in this chapter. Six cases of hypocalcaemic convulsions secondary to vitamin D deficiency were reported during the 1-year study period (May 2000 to April 2001) of the West Midlands study by Callaghan et al. (2006), equating to an annual incidence estimate of 1.88 per 100,000 children aged 0 to 4 years (confidence intervals not reported, but would be expected to be relatively wide given the small number of cases). There were 87 cases in this age group in the BPSU study, equating to an annual incidence of 1.00 per 100,000 children aged 0 to 4 years (95% CI: 0.80 to 1.23). Regional differences in ethnic demography

are the most likely explanation for incidence estimates being higher in the West Midlands study: in the 2011 census 7.3% of children aged 0 to 4 years in England & Wales were of Indian, Pakistani or Bangladeshi ethnic origin, compared to 13.6% in the West Midlands (ONS, 2013a). In the Scottish Paediatric Surveillance Unit study, 4 cases of hypocalcaemic seizures were reported during the 2-year study period between September 2009 to August 2011 (El-Fakhri et al, 2013). Although the authors do not report incidence estimates based on their results, using mid-2010 population estimates for Scotland (ONS, 2013c), an incidence estimate of 2.18 per million children aged 0 to 15 years (95% CI: 0.59 to 5.58) can be derived.

Internationally, incidence estimates for hypocalcaemic seizures due to vitamin D deficiency in children can be derived from the results of prospective national studies in Canada (Ward et al, 2007) and New Zealand (Wheeler et al, 2015), both of which used similar methods to the BPSU system with active surveillance of paediatricians. In the 2-year Canadian study (July 2002 to June 2004), the annual incidence of symptomatic vitamin D deficiency presenting to paediatricians was reported to be 2.9 per 100,000 children aged 0 to 17 years (95% CI: 2.2 to 3.7) (Ward et al, 2007). 19% of cases (n=20) presented with hypocalcaemic seizures, thus the annual incidence for this complication of vitamin D deficiency can be estimated at 5.5 per million children aged 0 to 17 years (95% CI: 3.4 to 8.6). In the New Zealand study, 8 children presented with hypocalcaemic seizures during the 3-year study period (July 2010 to June 2013) from an estimated population of 870,378 children below 15 years of age (Wheeler et al, 2015). Thus, an annual incidence of 3.06 per million children aged 0 to 14 years (95% CI: 1.32 to 6.04) can be calculated. There were 91 cases in this age group in the BPSU study, equating to an annual incidence of 3.73 per million children aged 0 to 14 years (95% CI: 3.00 to 4.58). In summary, national estimates for the incidence of hypocalcaemic seizures secondary to vitamin D deficiency among children in Canada and New Zealand are comparable to those for the UK described in this chapter.

The results of this study are consistent with previous reports in identifying children from South Asian and Black ethnic groups as being at highest risk of symptomatic vitamin D deficiency (Ahmed et al, 2011; Callaghan et al, 2006; El-Fakhri et al, 2013; Ladhani et al, 2004; Sharma et al, 2009). However, although rare, cases of severe vitamin D deficiency also occur in children from white ethnic backgrounds. Of the 11 cases with white ethnicity, two were adolescents with autistic spectrum disorders and restricted diets, one 2-year-old had multiple allergies and a restricted diet, and the remaining 8 were aged between 0 to 2 years without co-morbidities.

The age distribution of cases observed in this study is consistent with previous reports, which suggest that vitamin D deficiency presents with hypocalcaemic symptoms in two distinct age groups; infants aged between 0 to 2 years (the majority of cases) and adolescents (Ahmed et al, 2011; Ladhani et al, 2004). These age groups have been shown to correlate with periods of rapid growth, and it has been suggested that higher metabolic demand for calcium during periods of rapid bone growth may increase susceptibility for the development of hypocalcaemia (Ladhani et al, 2004).

Although most infants under 1 year of age were either exclusively breastfed or on mixed feeds, 15 cases were exclusively formula milk fed (19%). Almost all of the formula milk fed children were neonates under one month of age (n=14). Maternal vitamin D levels were available for 10 of these 14 cases, 70% of which were deficient (<25 nmol/L) and 30% insufficient (25-50 nmol/L). These results suggest that the vitamin D content of formula milk alone is not sufficient to prevent severe manifestations of vitamin D deficiency in neonates born to mothers with suboptimal vitamin D status during pregnancy. The vitamin D status of newborns is known to be directly dependent upon the vitamin D status of mothers during pregnancy (Thandrayen & Pettifor, 2012).

There was an unexpected male predominance in cases of 82%. However, a similar finding has been reported in two previous case series of hypocalcaemic seizures. A Turkish study of 93 infants aged between 1 to 24 months with hypocalcaemic seizures due to suspected rickets reported that 71% of cases were male (Bicakci, 2007). In a case series from the United States of 78 term neonates (age <31 days) with 'transient hypocalcaemia', 72% were male (Thomas et al, 2012). Cases in the American study exhibited suboptimal serum 25-OH-D levels (median 35 nmol/L), low magnesium levels (median 0.58 mmol/L), and inappropriately normal PTH levels (median 4.8 pmol/L). The authors proposed a synergistic role for transient hypoparathyroidism, vitamin D deficiency, and hypomagnesaemia in the aetiology of transient neonatal hypocalcaemia. The study was not able to explore reasons for the observed sex difference, however the authors hypothesised whether the explanation could involve gender-specific differences in neonatal vitamin D levels, PTH secretion, dietary calcium absorption, or an increased susceptibility of males to hypocalcaemic seizures. Case series of children with symptomatic vitamin D deficiency, including other manifestations such as rickets, have reported inconsistent results regarding gender. Some studies have reported a male predominance of between 55 – 64% (El-Fakhri et al, 2013; Robinson et al, 2006; Sharma et al, 2009), whilst other studies have reported equal numbers by sex (Ladhani et al, 2004; Ward et al, 2007). Studies investigating serum

25-OH-D levels in healthy neonates (Camargo et al, 2010), infants & toddlers (Gordon et al, 2008), and older children (Absoud et al, 2011; Mansbach et al, 2009) have not found any significant sex differences in vitamin D status. Thus, gender-specific differences in vitamin D levels do not appear to be the explanation for the observed male predominance in cases. In this study, the male predominance was present in both neonates (79%) and older children (84%). There was no significant difference in PTH levels between males and females (Table 4.7), suggesting that gender-specific differences in PTH response, or susceptibility to transient neonatal hypoparathyroidism, do not explain the observed male predominance in cases. Males have been reported to exhibit higher bone mineral content than females during early childhood (age 0 to 36 months) (Kalkwarf et al, 2014). Therefore, one possible hypothesis for the observed male predominance in cases is that that there may be gender-specific differences in metabolic calcium demand during periods of rapid bone growth, predisposing males to develop hypocalcaemia in the presence of vitamin D deficiency.

Median ALP and PTH levels were elevated, as is expected in the presence of metabolic bone disease due to vitamin D deficiency. However, phosphate levels were not depressed as is expected in vitamin D deficiency rickets, a finding previously reported in children with hypocalcaemic presentations of vitamin D deficiency (Ladhani et al, 2004). This is likely to be due to presentation in the early stage of vitamin D deficiency before a secondary hyperparathyroid response has been established or, as some authors have suggested, it may reflect PTH resistance in later stages of deficiency (Ladhani et al, 2004; Misra et al, 2008).

There were significant differences in serum biochemistry between cases presenting in the neonatal period and those presenting after 1 month of age. Older children generally exhibited an appropriate secondary hyperparathyroid response to the hypocalcaemia, with high PTH levels. In contrast, neonates exhibited lower PTH levels, with only 44% reported to have a PTH level ≥7.0 pmol/L. Neonates also exhibited lower ALP and higher phosphate levels compared to older children. These differences suggest that an inability of some neonates to mount an appropriate PTH response, possibly due to a transient neonatal hypoparathyroidism, may predispose this age group to a higher risk of developing hypocalcaemia in the presence of vitamin D deficiency.

There was a marked seasonal pattern in occurrence, with the majority of cases reported in and around the winter months, between late autumn (November) to early spring (April). This corresponds to periods in the year when levels of ultraviolet radiation from sunlight are at their lowest in the UK (DEFRA, 2016). Similar findings

have been reported by previous case series from Australia (Robinson et al, 2006) and Turkey (Cesur et al, 2011), in which hypocalcaemic presentations of vitamin D deficiency in children were predominantly seen in winter and spring. Whilst also reporting a seasonal pattern in the presentation of children with hypocalcaemic symptoms secondary to vitamin D deficiency, a case series from three London hospitals between 1996 to 2001 suggested that the peak occurs between March to July (spring to mid-summer), although the number of cases was relatively small (n=29) (Ladhani et al, 2004).

In the majority of cases, seizures were brief and self-terminating. Clinical outcomes were good, with no deaths reported. In a minority of cases (13%), it was reported that children did not receive vitamin D replacement in the form of treatment doses of colecalciferol or ergocalciferol, as recommended by national and international guidelines (Misra et al, 2008; RCPCH, 2013). 5 children received alfacalcidol only, 3 received a multivitamin (Abidec) only (at a dose of 0.6 ml/day, which equates to 400 units of ergocalciferol), and 2 cases received both alfacalcidol and Abidec. Among children who did receive colecalciferol or ergocalciferol, and for whom dosage information was available, 23% received a lower dose than recommended in the BNFc (2014). A surveillance study of symptomatic vitamin D deficiency in Scotland also reported considerable variation in management, with one third of cases receiving suboptimal doses of vitamin D in the form of multivitamin preparations (El-Fakhri et al, 2013).

### *4.6.2 Study Strengths*

The main strength of this study is the use of an established active surveillance system, with national coverage and consistently high response rates. A high proportion (~94%) of consultant paediatricians across the UK and Republic of Ireland participate in the BPSU reporting system (Knowles et al, 2012), therefore the results are nationally representative. The BPSU has a consistently high completion rate for reporting cards, providing some reassurance that the extent of any under-reporting of cases is unlikely to be large. Between 2011 and 2013, return rates for the BPSU 'Orange Card' ranged from 91.4% to 95.3% (BPSU, 2013; 2014).

### *4.6.3 Study Limitations*

This study is limited to one acute presentation of vitamin D deficiency, rather than investigating symptomatic vitamin D deficiency in children more broadly. Hence, the results do not indicate the overall health burden in children caused by symptomatic vitamin D deficiency. The rationale behind choosing to limit the study to hypocalcaemic seizures has been explained in section 4.2.2. In previous case series, between 4% to 27% of children presenting to secondary care with symptomatic vitamin D deficiency were reported to have hypocalcaemic seizures (Ahmed et al, 2011; Beck-Nielsen et al, 2009b; Callaghan et al, 2006; El-Fakhri et al, 2013; Ladhani et al, 2004; Sharma et al, 2009; Ward et al, 2007; Wheeler et al, 2015). This variation is explained by differences in study inclusion criteria, namely age.

Following the completion of this study, the BPSU relaxed their eligibility criteria regarding the maximum expected number of cases per year. Subsequently, a separate BPSU study of nutritional rickets presenting to secondary care was undertaken between March 2015 to March 2017. The final results from the study have not yet been published, however preliminary data indicated that 59 confirmed cases were identified in the first 13-months of surveillance (Julies & Blair, 2016).

Despite several reminders by post and email, and several attempts to contact paediatricians who did not respond by telephone, it was not possible to ascertain case status for a minority of reported cases (7%). This proportion is consistent with that of previous BPSU studies of between 5% to 14% (Adalat et al, 2014; Khalid et al, 2012; Williamson & Greene, 2010). The proportion of reported cases for which case status could not be ascertained increased from 3% in the first year of surveillance to 10% in the second year of surveillance. One possible explanation for this increase is the transition from postal to e-mail reporting during the study period (BPSU, 2013). The postal reporting cards contained an attached slip prompting paediatricians to note and keep the case identifiers (hospital number or name), which served as a reminder for clinicians when completing the questionnaire. However, there was no such reminder slip when electronic reporting cards were introduced. Thus paediatricians may have been less likely to keep a reminder of the case details when reporting cases, increasing the risk of clinicians being unable to recall the patient details when completing the questionnaire.

A degree of under-reporting is likely with any voluntary surveillance system, and therefore study incidence estimates are likely to be an underestimate of the true

incidence. However, the regular monthly intervals at which BPSU reporting cards are sent to participating paediatricians, along with reminders for non-response, serve to minimise under-reporting. As there was no alternative source available for case ascertainment, it is not possible to estimate the potential extent of under-reporting using capture-recapture methods (Knowles et al, 2006). Although Hospital Episode Statistics (HES) contains national data regarding hospital admissions in England, it uses the International Classification of Diseases (ICD) system to code diagnoses. As there are no specific codes for hypocalcaemic seizures in the ICD coding system, it was not possible to use HES data as a secondary source of case ascertainment for this study.

In some cases pathology other than vitamin D deficiency may have contributed to the development of hypocalcaemia, such as immaturity of the parathyroid axis in neonates as already discussed. Outside of the neonatal period one child had an inappropriately low PTH level suggesting hypoparathyroidism (0.3 pmol/L); a 5-month-old Pakistani male with radiological signs of rickets, a low 25-OH-D (10 nmol/L) and a raised ALP (2,895 iu/L).

### *4.6.4 Conclusions*

Hypocalcaemic seizures are a rare complication of vitamin D deficiency in children in the UK and Ireland. The national incidence is similar to estimates from other developed countries with populations of majority Caucasian ethnicity (Canada and New Zealand). Children from high-risk ethnic backgrounds are disproportionately affected; the incidence is approximately 1 in every 3,300 infants of South Asian origin under one year of age, and 1 in every 3,700 infants of black ethnicity. Although uncommon, clinical complications of vitamin D deficiency such as hypocalcaemic seizures are preventable through vitamin D supplementation. This study supports the findings of previous case series in suggesting that the current implementation of public health policy in the UK is not preventing children, particularly those from high-risk backgrounds, from developing severe manifestations of vitamin D deficiency. The implications of the work described in this chapter, with respect to clinical practice, public health policy and future research, are further discussed in the final chapter of the thesis.

# Chapter 5

# Time Trends and Determinants for the Diagnosis of Vitamin D Deficiency in UK Children: A Cohort Study Using Primary Care Electronic Health Records

## 5.1 Introduction

Vitamin D has attracted considerable clinical and academic interest over the last two decades. Anecdotal reports and local case series have suggested an increase in the number of children presenting to paediatric services in the UK with symptomatic complications of deficiency, and a large body of observational research has stimulated debate regarding the postulated role of vitamin D deficiency in the development of various non-musculoskeletal diseases. As vitamin D has attracted increasing attention, large increases in vitamin D testing and prescribing have been reported in adult practice. However, there has not been any empirical investigation of rates of diagnosis of vitamin D deficiency in clinical practice, either in the UK or internationally. This chapter describes a cohort study undertaken to determine longitudinal trends in the diagnosis of vitamin D deficiency in children in the UK.

## 5.2 Aims and Objectives

### *5.2.1 Study Aims*

The overall aims of this study were to explore longitudinal trends in the diagnosis of vitamin D deficiency among children in UK clinical practice over the past 15 years, and examine differences by socio-demographic characteristics.

### *5.2.2 Study Objectives*

i) To determine rates of diagnosis of vitamin D deficiency in children in the UK in each year between 2000 to 2014.

ii) To explore differences in rates of diagnosis of vitamin D deficiency in UK children by age, sex, ethnicity, socio-economic position, and geographical area.

iii) To examine the recording of symptoms, in the primary care health record, among children diagnosed with vitamin D deficiency.

## 5.3 Methods

### *5.3.1 Study Design*

A cohort study using UK primary care electronic health records, held in The Health Improvement Network (THIN) database.

### *5.3.2 Data Sources*

#### *5.3.2.1 The Health Improvement Network (THIN) Database*

THIN is a large longitudinal database containing anonymised patient-level electronic medical records from primary care in the UK, and has been widely used for epidemiological research (http://www.epic-uk.org/bibliography/bibliography_01.shtml, accessed 22/09/2016). Routine consultation data is collected from participating general practices that use Vision computer software (In Practice Systems Ltd) to manage patient consultations and health records. The anonymised patient data is collected and processed for research use by IMS Health Inc., which performs various internal validity checks before supplying the THIN data to researchers (http://www.epic-uk.org, accessed 22/09/2016).

The database contains information recorded in patients' electronic medical records as part of their routine clinical care, including medical diagnoses, symptoms, medication prescriptions, and laboratory test results. Medical diagnoses and symptoms are recorded using a hierarchical coding system known as Read codes, which was developed for use in UK primary care, includes more than 100,000 codes, and can be mapped to the International Classification of Diseases, Tenth Edition (ICD-10) (Booth, 1994; Davé & Petersen, 2009). Medication prescriptions in primary care are particularly well recorded in THIN, as they are issued electronically by general practitioners (GPs) and automatically captured in the electronic patient record (Thiru et al, 2003). Further consultation details are entered by GPs as free text, which is not routinely available to researchers but can be purchased following anonymisation by IMS Health staff. As GPs act as gatekeepers in primary care to secondary healthcare services in the UK, diagnoses made in secondary care can also be captured, from information contained in discharge summaries and outpatient letters. Information in patient-related

correspondence from secondary care that is deemed to be important may be coded into the primary care electronic health record by GPs or practice administrative staff.

THIN also contains information regarding patients' demographic characteristics. For children below 15 years of age at the time of the data release, year and month of birth are available, whilst year of birth is available for older individuals. Sex, date of practice registration, date of transfer out of practice, and date of death are recorded. Information regarding ethnicity and area-based measures of social deprivation are also recorded, albeit with incomplete coverage (Mathur et al, 2014). THIN also contains a 'household' identifier, which is identical for individuals who are registered with the same practice and have a matching first line of address at the time of patient registration with the practice. In some circumstances, however, the same 'household' identifier can encompass multiple households and contain a large number of individuals. For example, blocks of flats and university halls of residence can be covered under one address and share a single 'household' identifier in the dataset. Information regarding the geographical location of practices is available, at the level of former strategic health authorities (SHAs) for practices in England, and at country level for practices in Scotland, Wales, and Northern Ireland. SHAs were part of the organisational structure of the NHS in England between 2002 and 2013, responsible for management of health services at a regional level (Boyle, 2011). Between 2006 and 2013, England was divided into 10 SHA regions (Figure 5.1). SHAs were abolished in 2013, and replaced by a new NHS organisational structure.

The vast majority of the UK population is registered with a general practice, although accurate estimates for this proportion are not available. The total number of registered patients in England in 2015 (56.9 million) was greater than the overall population estimate (54.8 million) (HSCIC, 2015a; ONS, 2016). There are various reasons for this discrepancy including over-counting in GP registers (e.g. double-counting of individuals registered with more than one practice, or counting of 'ghost' patients who died or migrated out of the country without being removed from the GP register), and the registration of short-term migrants, who are not included in population estimates, with GPs. The THIN cohort has been shown to be broadly representative of the UK population as a whole in terms of age and sex distribution (Blak et al, 2011). However, it is somewhat over-representative of individuals from more affluent areas, as measured by the postcode-based Townsend deprivation index; in analysis of THIN patients actively registered in 2009, 23.5% were recorded in the most affluent quintile, whilst only 14.6% belonged to the least affluent quintile (20% in each quintile nationally) (Blak et al, 2011). Recording of consultations and prescriptions in THIN

practices is comparable to national primary care statistics (Bourke et al, 2004). The prevalence of various chronic medical conditions, and mortality rates adjusted for social deprivation, in THIN are similar to UK national statistics (Blak et al, 2011). Well-established associations between risk factors and a number of common diseases (stroke, myocardial infarction, bowel cancer, and peptic ulcer disease) have been replicated using THIN data (Lewis et al, 2007).

For the analysis reported in this chapter, the February 2015 release of THIN data was used. This contains the medical records of 11.6 million patients in total, registered with 641 general practices in the UK, from 3rd June 1985 up to 10th February 2015. 3.9 million patients were actively registered in 2014, representing 5.96% of the UK population as a whole.

**Figure 5.1** Strategic health authorities (SHAs) in England, between 2006 to 2013.


Figure adapted from: Department of Health (2016) *Strategic Health Authority Configurations*. Available at https://web.archive.org/web/20070130014013/http://www.dh.gov.uk/assetRoot/04/13/37/60/04133760.pdf [Accessed 23rd November 2016].

#### 5.3.2.2 Hospital Episode Statistics (HES)

For a subset of the THIN practices in England, linked patient-level Hospital Episode Statistics (HES) data is available. HES is an administrative dataset containing details of all care episodes at NHS hospitals in England, including inpatient admissions, outpatient appointments and accident and emergency (A&E) attendances (http://digital.nhs.uk/hes, accessed 23/09/2016). Each hospital submits data from its own Patient Administration System to the centralised HES data warehouse, which is then validated and cleaned by NHS Digital (formerly called the Health and Social Care Information Centre, HSCIC), according to a pre-specified list of rules. HES data includes clinical information regarding diagnoses (recorded using the ICD-10 classification) and operations, however this is only consistently recorded for inpatient admissions data (primary diagnosis was recorded for 100% of admissions in the 2011-2012 financial year) (HSCIC, 2013b). Recording of clinical diagnoses is very limited in the outpatient data (4.1% of attendances in the 2011-2012 financial year) and A&E data (49.2% of attendances in the 2011-2012 financial year) (HSCIC, 2012; 2013a). Demographic information regarding ethnicity is also recorded in HES.

Linkage of THIN and HES data was performed by Cegedim Strategic Data Medical Research UK (which supplied the THIN database at the time of this study, subsequently acquired by IMS Health Inc.), in collaboration with Sapior, a third party that developed the encryption technology for linkage (CSDMRUK, 2014). This involved probabilistic linkage using the NHS number, date of birth and sex (personal communication with IMS Health, 2016). The linkage methodology involved encryption of patient identifiers (in both the primary care records and HES data) to create 'encryption keys', followed by upload of the encrypted data to a secure website where matching keys were linked. This enabled linkage without the need for export of patient identifiable data from the data providers (THIN practices and HSCIC). 75.7% of actively registered patients from participating THIN practices were linked to one or more event in HES (CSDMRUK, 2014). Among the patients who were not matched, it is not known what proportion had used hospital services but were failed matches, and what proportion had truly never used secondary care services. Thus, the overall completeness of the linkage is not known. Among patients who matched to one or more HES records, 95% had a one-to-one match on the NHS number without any data discrepancies (duplicate matches in either dataset, or conflicting data regarding sex or date of birth across the datasets).

The coding of clinical information from case notes into diagnostic codes for HES is undertaken by administrative staff, rather than clinical staff. Hence, the accuracy of HES data has been questioned, particularly with regard to differences in coding practices between hospitals (Williams & Mann, 2002). A systematic review of studies comparing the agreement of coded discharge diagnoses in HES with either independent case note reviews or clinical registry data reported a median agreement of 80.3% (IQR 63.3% to 88.7%) (Burns et al, 2012).

At the time that the work described in this chapter was undertaken, linked HES inpatient and outpatient data was available for 156 THIN practices in England (24% of all THIN practices). However, HES A&E data was not provided to researchers. The linked HES data covered the time period 1st April 1997 to 31st March 2012, and therefore did not overlap entirely with the period for which THIN data was available.

### *5.3.3 Study Population*

#### *5.3.3.1 Inclusion and Exclusion Criteria*

The study population included children aged between 0 to 17 years, who were actively registered with a THIN practice between 1st January 2000 and 31st December 2014.

IMS Health runs internal validation checks of the patient records for each individual in THIN, and assigns each patient an indicator (Patflag) for the integrity of data in their record (CSDMRUK, 2010). Only individuals with an acceptable patient record status (Patflag A or C) were included; this excludes individuals with data missing for year of birth, sex, or date of registration, patients who are not permanently registered with the practice, and patients with out of sequence data records (e.g. year of birth later than year of registration, or registration date after date of leaving the practice).

Children with a record meeting the case definition for diagnosis of vitamin D deficiency (see section 5.3.4.1) prior to their date of entry to study follow-up (see section 5.3.3.2) were excluded, as they represent prevalent rather than incident cases. For the main analyses, children with a record of a medical condition that can predispose to vitamin D deficiency by interfering with vitamin D absorption or metabolism (chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption; see section 5.3.6.8) were excluded, as routine screening of vitamin D status is expected in children with these conditions.

#### 5.3.3.2 Entry to Study Observation Period

The study cohort was open (dynamic), meaning that children entered and exited the cohort at different time points. Therefore, they were observed over different periods of time, and contributed different lengths of follow-up to the study.

The date of entry into the cohort for each individual, i.e. the start of their period of observation (follow-up), was set as the latest of the following dates:

i) Start of the study period (1st January 2000).

ii) Date of registration with the GP practice, for children under one year of age at the time of registration.

iii) Date of registration with the GP practice plus 3 months, for children ≥1 year of age at the time of registration (see below for explanation).

iv) The date when the practice met pre-defined criteria for acceptable mortality recording (AMR date, see below).

v) The date when the practice met pre-defined criteria for acceptable computer usage (ACU date, see below).

Diagnoses recorded in primary care databases shortly after the time of patient registration with a practice can represent historical information transferred from the patient's medical record, rather than incident events. Lewis and colleagues (2005) demonstrated that recorded incidence rates for a variety of conditions were higher than baseline during an initial time period after practice registration, and that the length of this time period varied depending on the nature of the condition (generally up to 3 months for acute conditions, and up to 1 year for chronic conditions). Failure to exclude this time period from study follow-up can result in the misclassification of prevalent cases as incident, and overestimation of incidence rates. Plots of incidence rates of the outcome against time since registration (Lewis plots) were used to explore whether there was evidence of greater recording of vitamin D deficiency diagnosis in the initial period after practice registration (Lewis et al, 2005). These results, described in section 5.4.1, demonstrated that rates of recorded diagnosis were greatest in the first 3 months after registration, and reached baseline after 9 months following registration. In the main analyses, for children aged ≥1 year at the time of practice registration, the first 3 months after registration were excluded from follow-up. A sensitivity analysis was

performed to explore the influence of varying this period of exclusion from between 0 to 9 months after practice registration. The period of exclusion was not necessary for infants under one year of age, for whom any recorded diagnoses can be considered incident (regardless of proximity to registration) as they will have occurred within the preceding year.

The acceptable mortality recording (AMR) and acceptable computer usage (ACU) criteria are previously developed data quality indicators for electronic data recording in UK primary care databases (Horsfall et al, 2013; Maguire et al, 2009). They were developed to identify periods of incomplete use of computerised medical record systems by general practices in primary care data, e.g. following the transition from paper to electronic patient records, and are widely used for defining periods of follow-up in studies using THIN data (Horsfall et al, 2014; Sharma et al, 2016; Sheehan et al, 2015). The AMR date identifies the time from which the observed mortality for each practice is similar to expected mortality, based upon national mortality rates applied to the age and sex structure of the practice population (Maguire et al, 2009). The ACU date identifies the time from which average annual recording rates for consultations, health measurements, and prescriptions for each practice meets pre-specified criteria (on average at least two therapy records, one medical record, and one additional health data record per patient per year) (Horsfall et al, 2013). Use of the AMR and ACU criteria have been shown to produce trends over time in disease incidence rates and antibiotic prescription rates in THIN that more closely match trends obtained from external data sources (Horsfall et al, 2013). The study start date was chosen as 1$^{st}$ January 2000, as prior to this year less than half of THIN practices had achieved ACU (Horsfall et al, 2013). From 2003 onwards, over 90% of THIN practices meet both AMR and ACU criteria.

#### 5.3.3.2 Exit from Study Observation Period

The date of exit from the cohort for each individual was set as the earliest of the following dates:

i) Mid-point of 18th year after birth.

ii) Date of transfer out of the practice.

iii) Date when the practice stopped contributing data to THIN.

iv) Date of death.

v) End of the study period (31st December 2014).

vi) The date of the earliest entry in the patient's medical record meeting the case definition for diagnosis of vitamin D deficiency (see section 5.3.4.1).

The mid-point of the 18th year after birth was used, as opposed to the 18th birthday, because exact dates of birth are not provided in THIN in order to protect patient confidentiality. Month of birth is provided for children below 15 years of age at the time of the data release, whilst for older individuals only year of birth is available.

### *5.3.4 Outcome*

The primary outcome was diagnosis of vitamin D deficiency.

#### 5.3.4.1 Case Definition

For the main analyses, diagnosis of vitamin D deficiency was defined as a record of any one of the following three criteria in the primary care electronic medical record (THIN):

i) A Read code related to vitamin D deficiency or rickets (see section 5.3.6.2).

ii) Prescription of vitamin D (calciferol) at a 'treatment dose' (see sections 5.3.4.2, 5.3.6.4 and 5.3.7.1).

iii) A serum 25-hydroxyvitamin D (25-OH-D) test result with a value of <25 nmol/l (see sections 5.3.4.3, 5.3.6.5, and 5.3.7.2).

Analysis of UK primary care electronic health data has shown that GPs do not always record medical diagnoses using Read codes (Ford et al, 2013). In some cases, information regarding diagnosis is only entered as free text. Free text records are not routinely available to researchers using THIN data, as manual data cleaning to ensure removal of any potentially identifiable information must first be undertaken by IMS Health staff. Using diagnosis Read codes alone to identify cases from primary care data can therefore result in case under-ascertainment, and underestimation of disease incidence or prevalence. For this reason, vitamin D prescriptions and test results were also included in the case definition, in order to capture children who had been identified with or treated for vitamin D deficiency without the diagnosis having been recorded using Read codes.

A sensitivity analysis was performed to explore the influence of using linked HES inpatient data as an additional source for case ascertainment. The study population for this analysis was limited to individuals registered with THIN practices for which linked HES data was available. The time period for which complete years of linked HES data were available limited the study period for this analysis to follow-up between 1st January 2000 and 31st December 2011. For this analysis, the case definition was a record of any one of the following four criteria:

i) A Read code related to vitamin D deficiency or rickets, in the THIN patient record.

ii) Prescription of vitamin D (calciferol) at a 'treatment dose', in the THIN patient record.

iii) A serum 25-hydroxyvitamin D (25-OH-D) test result with a value of <25 nmol/l, in the THIN patient record.

iv) An ICD-10 code related to vitamin D deficiency or rickets, in the HES inpatient record (see section 5.3.6.3).

#### *5.3.4.2 Definition of 'Treatment Dose' for Vitamin D Prescriptions*

Although there are numerous different treatment regimens for vitamin D deficiency in children, doses recommended for the treatment of established deficiency tend to be considerably larger than those used for supplementation or prevention of deficiency (prophylaxis). The British National Formulary for Children (BNFc) advises that

colecalciferol or ergocalciferol are used for the treatment of established deficiency, with the following dosage by age (BNFc, 2014):

| | |
|---|---|
| 1-5 months: | 3,000 International Units (IU) per day |
| 6 months to 12 years: | 6,000 IU per day |
| >12 years: | 10,000 IU per day |

The BNFc does not specify a dose for neonates under 1 month of age, however guidance from the Royal College of Paediatrics and Child Health (RCPCH) recommends doses of between 1,000 to 3,000 IU per day in this age group (RCPCH, 2013). The recommended length of treatment with the above 'pharmacological' doses of vitamin D is generally between 1 to 3 months, after which it is advised that children take low-dose maintenance treatment long-term (Misra et al, 2008; Munns et al, 2016; RCPCH, 2013; Shaw & Mughal, 2013a).

As an alternative strategy to daily dosing, vitamin D deficiency can be treated with a large dose of calciferol given as either a single dose, or in divided doses over a short period of time. This is known as stoss therapy, and typically involves the administration of doses between 100,000 to 600,000 IU, either orally or by intramuscular injection (Misra et al, 2008; Munns et al, 2016; Pearce & Cheetham, 2010).

Prophylactic doses of vitamin D recommended for the prevention of vitamin D deficiency, or maintenance of vitamin D levels after completion of treatment for deficiency, are considerably lower than 'pharmacological' treatment doses; between 400 to 1,000 IU per day in children, and 800 to 2,000 IU per day in adults (BNFc, 2014; Misra et al, 2008; Munns et al, 2016; Pearce & Cheetham, 2010; RCPCH, 2013).

For the case definition, the intention was to choose dosage criteria that would capture prescriptions of vitamin D issued for the treatment of established deficiency, but would exclude prescriptions at lower doses compatible with supplementation or maintenance therapy. Only prescriptions for pure preparations of calciferol (colecalciferol or ergocalciferol) were included in the case definition, as this is the form of vitamin D recommended for the treatment of primary vitamin D deficiency (BNFc, 2014; Shaw & Mughal, 2013a). Activated analogues of vitamin D, such as alfacalcidol and calcitriol, were not included as these are not routinely recommended for the treatment of primary vitamin D deficiency, and are generally used in situations where vitamin D metabolism is impaired (e.g. chronic renal impairment) or in hypoparathyroidism (see chapter 2.3.3). Cod liver oil or multivitamin preparations containing vitamin D were not included in the case definition, as the calciferol content of these products when taken at

recommended doses represents prophylactic doses of vitamin D. The distribution of prescribed dosage for records of combined calcium and vitamin D preparations in the study cohort was explored. The prescribed dose was <1,000 IU/day in over 99% of these records. Therefore, combined calcium and vitamin D preparations were considered to represent prophylactic / maintenance therapy, and were excluded from the case definition.

The BPSU surveillance study of hypocalcaemic seizures secondary to vitamin D deficiency described in chapter 4, and other published case series (El-Fakhri et al, 2013), have demonstrated considerable variation in the treatment of established vitamin D deficiency in clinical practice. Almost a quarter of cases reported to the BPSU study were treated with doses of vitamin D lower than those recommended in the BNFc (see chapter 4.5.8). Therefore, it was predicted that setting the dosage thresholds for the case definition at the BNFc recommended doses could risk missing children with established deficiency who were treated with lower doses of vitamin D. For the main analyses, the following definition for 'treatment dose' of vitamin D was used:

- Daily dose of ≥1,500 IU per day if age <6 months
- Daily dose of ≥3,000 IU per day if age 6 months to 12 years
- Daily dose of ≥5,000 IU per day if age >12 years
- One-off (stoss) dose of ≥100,000 IU at any age

These age specific thresholds for daily dosage represent half of the recommended doses in the BNFc, and are greater than doses recommended for prophylaxis or maintenance. A sensitivity analysis was performed using a range of alternative definitions for 'treatment dose' vitamin D, to explore the influence of the choice of dosage thresholds on the outcome:

a) Lower alternative definition for 'treatment dose' vitamin D:

- Daily dose of ≥1,000 IU per day if age <6 months
- Daily dose of ≥2,000 IU per day if age 6 months to 12 years
- Daily dose of ≥3,000 IU per day if age >12 years
- One-off (stoss) dose of ≥100,000 IU at any age

b) Higher alternative definition for 'treatment dose' vitamin D:

- Daily dose of ≥3,000 IU per day if age <6 months
- Daily dose of ≥6,000 IU per day if age 6 months to 12 years
- Daily dose of ≥10,000 IU per day if age >12 years
- One-off (stoss) dose of ≥100,000 IU at any age

#### *5.3.4.3 Rationale for the Choice of the 25-OH-D Test Threshold*

The evidence base underpinning the level of serum 25-hydroxyvitamin D used to define vitamin D deficiency is limited, and various thresholds representing 'deficiency' and 'sufficiency' are used internationally (see chapter 2.4). However, in the UK most clinical guidelines are consistent in defining biochemical vitamin D deficiency as a 25-OH-D level below 25 nmol/l (Arundel et al, 2012; Pearce & Cheetham, 2010; RCPCH, 2013; Shaw & Mughal, 2013b). It is likely that the majority of clinical biochemistry departments will report 25-OH-D results using this cut-off, and therefore that GPs will base their interpretation of 25-OH-D test results on this threshold.

### *5.3.5 Covariates*

The following study covariates were included in analyses exploring associations with rates of diagnosis of vitamin D deficiency: sex, age, ethnicity, indices of deprivation, geographical area (country, and strategic health authority in England), and calendar time.

#### *5.3.5.1 Age*

For children aged below 15 years at the time of the data release (February 2015), year and month of birth were available, and date of birth was taken to be the 15$^{th}$ day of the month of birth. For individuals aged 15 years or older at February 2015, only year of birth was available, and date of birth was taken to be the 30$^{th}$ of June on the year of birth. For analyses exploring associations with the outcome, age was categorised into four groups: 0 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 17 years.

#### 5.3.5.2 Ethnicity

Information regarding ethnicity was derived from relevant Read codes in THIN and augmented by ethnicity records in linked HES data (see sections 5.3.6.6 and 5.3.7.3). In order to further minimise missing data, maternal ethnicity was used as a proxy measure for children's ethnicity for children without an ethnicity record available.

Ethnicity is recorded in HES using the Office for National Statistics (ONS) 2001 Census classification (Table 5.1), and relevant Read codes in THIN were also categorised using this classification (see appendix G.2) (ONS, 2001). Ethnicity recorded at any point in time in the patient record was included, including records outside of the study observation period.

**Table 5.1** ONS 2001 Census classification of ethnicity.

| Level 1 (5-category) classification | Level 2 (16-category) classification |
|---|---|
| White | White British |
| | Irish |
| | Other White background |
| Mixed | White and Black Caribbean |
| | White and Black African |
| | White and Asian |
| | Other mixed background |
| Asian or Asian British | Indian |
| | Pakistani |
| | Bangladeshi |
| | Other Asian background |
| Black or Black British | Caribbean |
| | African |
| | Other Black background |
| Chinese or Other Ethnic Groups | Chinese |
| | Other ethnic group |

Previous work has suggested that ethnicity data in healthcare records is more reliable when collapsed into broader (higher-level) categories compared to more detailed (lower-level) categories. The level of discordance between recorded ethnicity in HES and patients' self-reported ethnicity was shown to be greater when ethnicity was

categorised using a 16-group classification (4.9% overall discordance) compared to a 6-group classification (1.4% overall discordance) (Saunders et al, 2013). Of note, the difference was more marked when considering patients from minority groups. Discordance with self-reported ethnicity was 24% among patients with HES ethnicity recorded as Indian, Pakistani, Bangladeshi, or other Asian background. However, when ethnicity was classified using the broader category of 'Asian or British Asian', discordance was lower at 11%. Similarly, discordance with self-reported ethnicity was 32% among patients with HES ethnicity recorded as Caribbean, African, or other black background, compared to 15% when ethnicity was classified using the broader category of 'Black or Black British'. Within the study cohort, the consistency of ethnicity data within individual patients' records (THIN and HES) was greater when the higher-level classification of ethnicity was used. Among children with ethnicity data available, the proportion who had multiple ethnicity records belonging to different categories was 5.5% using the 5-level classification compared to 9.8% using the 16-level classification. In view of the above evidence, it was considered that the accuracy of ethnicity data in routine healthcare records may not be sufficient to allow reliable analysis at the more detailed 16-category level, and therefore the broader 5-category classification was used for all subsequent analyses.

#### *5.3.5.3 Measures of Socio-Economic Position*

Two area-based measures of socio-economic position are available in the THIN database; the Townsend Index and the Index of Multiple Deprivation (IMD). Values for these measures are linked to individual patient records in THIN using patients' postcodes. The Townsend Index was derived from 2001 Census data at the level of the Census output area (average number of households in each area 124, average number of people in each area 297), and is available for patients from practices throughout the UK (ONS, 2012). The Townsend Index is calculated by summing the standardised scores of 4 variables (Townsend et al, 1988):

- The percentage of households without access to a car.
- The percentage of households not in owner occupied accommodation.
- The percentage of households in overcrowded accommodation.
- The percentage of the economically active population aged 16-74 years who are unemployed.

The resulting scores are grouped into 5 quintiles, from 1 (least deprived) to 5 (most deprived).

The Index of Multiple Deprivation is a composite score derived from 37 indicators across 7 domains (ODPM, 2004):

- Income deprivation.
- Employment deprivation.
- Health deprivation and disability.
- Education, skills and training deprivation.
- Barriers to housing and services.
- Living environment deprivation.
- Crime.

The majority of the indicators relate to data collected in 2001. The resulting scores are again grouped into 5 quintiles. The IMD is measured at the lower layer super output area level (average number of households in each area 630, average number of people in each area 1,514) (ONS, 2012).

As the IMD is only available for patients from THIN practices in England, this variable was only included in analyses limited to THIN practices that have linked HES data available (the linked THIN-HES study cohort). The Townsend Index was used both for analyses using the full THIN study cohort as well as the linked THIN-HES study cohort.

### *5.3.6 Code List Development*

#### *5.3.6.1 Strategy for Code List Development*

Previously reported guidelines were used to compile Read code lists and drug code lists for all outcomes and covariates of interest (Davé & Petersen, 2009). The development of Read code lists involved the following steps:

1) Compilation of a list of key words and synonyms for the condition of interest. Key words were truncated to produce terms which capture multiple related words, e.g. the truncated term *depress* captures the words ‘depression’, ‘depressed’, and ‘depressive’.

2) Searching the Read code dictionary for code descriptions containing these key terms, at any location within the code description.

3) Review of the codes identified by the above word search, and identification of common code stems among relevant codes. Due to the hierarchical nature of the Read coding system, related codes are often grouped together under common stems.

4) Searching the Read code dictionary for any additional codes beginning with the relevant code stems identified above.

5) Manual review of all identified codes, and exclusion of any irrelevant codes.

Prescribed drugs are recorded in THIN using the Multilex coding system (http://www.firstdatabank.co.uk), with the Multilex drug codes encrypted. Each drug code is linked to a description of the drug's generic name, and some codes are linked to the British National Formulary (BNF) chapter that the drug appears in. Brand names (also called proprietary or trade names) are not made available. The development of drug code lists involved the following steps:

1) Manual review of all drug codes listed under the BNF chapter(s) that are felt to be relevant to the drug of interest.

2) Compilation of a list of truncated key words and synonyms for the drug of interest.

3) Searching the drug code dictionary for code descriptions containing these key terms, at any location within the code description.

4) Manual review of all identified codes, and exclusion of any irrelevant codes.

The following steps were used to develop ICD-10 code lists (for the identification of medical diagnoses recorded in linked HES data):

1) Compilation of a list of truncated key words and synonyms for the condition of interest.

2) Searching the ICD-10 code dictionary for code descriptions containing these key terms, at any location within the code description.

3) Review of the codes identified by the above word search, and identification of common code stems among relevant codes.

4) Searching the ICD-10 code dictionary for any additional codes beginning with the relevant code stems identified above.

5) Manual review of all identified codes, and exclusion of any irrelevant codes.

#### *5.3.6.2 Identification of Read Codes Related to Vitamin D Deficiency and Rickets*

The following truncated search terms were used to identify Read codes related to vitamin D deficiency and rickets: 'ricket', 'rachit', 'vitamin d', 'vit d', 'calciferol', 'osteomalacia', 'vitaminosis'. Common code stems were used to identify additional relevant codes. Codes for rare inherited causes of rickets (e.g. 'x-linked hypophosphataemic rickets'), and rickets related to underlying chronic diseases associated with impaired vitamin D absorption or metabolism (e.g. 'renal rickets', and 'coeliac rickets'), were excluded. The final list of included codes is shown in Table 5.2.

**Table 5.2** Read codes related to vitamin D deficiency and rickets.

| Read code | Description |
|---|---|
| C28..00 | Vitamin D deficiency |
| C28..12 | Rickets |
| C280.00 | Active rickets |
| C28z.00 | Avitaminosis D NOS |
| C28..11 | Osteomalacia |
| C282.00 | Osteomalacia unspecified |

From 2013 onwards, a new code for 'Vitamin D insufficiency' (C2B..00) was added to the Read code dictionary. A sensitivity analysis was performed to explore the influence of additionally including this code on the results.

#### *5.3.6.3 Identification of ICD-10 Codes Related to Vitamin D Deficiency and Rickets*

The following truncated search terms were used to identify ICD-10 codes related to vitamin D deficiency and rickets: 'ricket', 'rachit', 'vitamin d', 'vit d', 'calciferol', 'osteomalacia', 'vitaminosis'. Common code stems were used to identify additional relevant codes. Codes referring to 'senile osteomalacia', 'adult osteomalacia', and 'puerperal osteomalacia' were excluded as they refer to conditions in adulthood or

related to pregnancy. Codes referring to 'drug-induced' osteomalacia were excluded as they do not refer to primary vitamin D deficiency. The code E643, 'sequelae of rickets', was excluded as the code description suggests a historical diagnosis. The final list of included codes is shown in Table 5.3.

**Table 5.3** ICD-10 codes related to vitamin D deficiency and rickets.

| ICD-10 code | Description |
|---|---|
| E550 | Rickets, active |
| E559 | Vitamin D deficiency, unspecified |
| E55X | Vitamin D deficiency |

#### *5.3.6.4 Identification of Drug Codes Referring to Pure Preparations of Calciferol*

All drug codes linked to the BNF chapter for vitamin D ('09.06.04': BNF/Nutrition and blood/Vitamins/Vitamin D) were manually reviewed, and codes that referred to a pure preparation of colecalciferol, ergocalciferol, or calciferol (type not specified) were included. Additional relevant codes were identified by searching the drug code dictionary for code descriptions containing the following truncated key terms; 'calciferol', 'colecal', 'cholecal', 'ergocal', 'vitamin d'. Drug codes referring to combined calciferol and calcium preparations, multivitamins, cod liver oil, and activated analogues of vitamin D were excluded (see section 5.3.4.2). A total of 246 drug codes referring to pure preparations of calciferol were identified (see appendix G.1).

#### *5.3.6.5 Identification of Read Codes Related to Vitamin D Tests*

The following truncated search terms were used to identify Read codes referring to vitamin D tests; 'vitamin d', 'vit d', 'calciferol', '25-OH-D', '25(OH)D', '25OHD', '250HD', '25-0H-D', '25(0H)D'. Common code stems were used to identify additional relevant codes. Codes referring to levels of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, combined total 25-hydroxyvitamin D2 and D3, 25-hydroxyvitamin D (type not specified), and unspecified vitamin D were included. Codes referring to 1,25-dihydroxyvitamin D tests were excluded, as levels of the biologically active hormone are not used to assess an individual's vitamin D status. The final list of included codes is shown in Table 5.4.

**Table 5.4** Read codes related to vitamin D tests.

| Read code | Description |
|---|---|
| 44LA.00 | Serum vitamin D |
| 44Lg.00 | Serum vitamin D2 level |
| 44LM.00 | Plasma 25-Hydroxyvitamin D3 level |
| 44Ln.00 | Serum 25-Hydroxyvitamin D2 level |
| 44LP.00 | Serum 25-Hydroxy vitamin D3 level |
| 4QB4.00 | Vitamin D level |
| 4QB4000 | Vitamin D2 level |
| 4QB4100 | Vitamin D3 level |
| 4QB4200 | 25-Hydroxyvitamin D2 level |
| 4QB4300 | 25-Hydroxyvitamin D3 level |
| 4QB4400 | Combined total vitamin D2 and D3 level |
| 4QB4500 | 25-Hydroxyvitamin D level |
| 4QB4600 | Total 25-hydroxyvitamin D level |
| 4QB4700 | Serum total 25-hydroxy vitamin D level |
| 5788.00 | Radiobioassay - vitamin D |

#### *5.3.6.6 Identification of Read Codes Related to Ethnicity*

The following truncated search terms were used to identify Read codes related to ethnicity, nationality, country of birth, or language: ‘ethn’, ‘census’, ‘nationality’, ‘country’, ‘origin’, ‘race’, ‘born in’, ‘language’, ‘interpreter’, ‘white’, ‘black’, ‘asian’, ‘british’, ‘irish’, ‘africa’, ‘caribbean’, ‘india’, ‘pakistan’, ‘bangladesh’, ‘chinese’. Common code stems were used to identify additional relevant codes. Relevant codes were grouped into three categories:

1) Codes referring to ethnicity, nationality, or race.
2) Codes referring to country of birth.
3) Codes referring to spoken or read language, or the need for an interpreter.

A total of 954 relevant codes were identified, each of which were manually reviewed and coded according to the ONS 2001 Census 5-category and 16-category classifications (see appendix G.2). An assumption was made that the code for ‘British or mixed British’ represents White British ethnicity.

#### *5.3.6.7 Identification of Read Codes Related to Pregnancy or Delivery*

The following truncated search terms were used to identify Read codes related to pregnancy or delivery: ‘pregnan’, ‘antenatal’, ‘a/n’, ‘ante natal’, ‘matern’, ‘birth’, ‘born’,

'delivery', 'caesarean', 'c section', 'c-section', 'baby', 'labour', 'postnatal', 'p/n', 'post natal', 'fetal'. Common code stems were used to identify additional relevant codes. Codes referring to stillbirth, miscarriage, or neonatal death were excluded. A total of 751 relevant codes were identified (see appendix G.3).

#### *5.3.6.8 Identification of Read Codes Related to Liver Disease, Chronic Kidney Disease, and Conditions Associated with Gastrointestinal Malabsorption*

The following truncated search terms were used to identify Read codes related to liver disease: 'liver failure', 'liver disease', 'liver transplant', 'hepatic failure', 'hepatic disease', 'cirrhosis', 'biliary atresia', 'kasai', 'alagille', 'antitrypsin', 'budd chiari', 'sclerosing cholangitis', 'hepatitis', 'haemochromatosis'. Common code stems were used to identify additional relevant codes. A total of 283 relevant codes were identified (see appendix G.4).

The following truncated search terms were used to identify Read codes related to chronic kidney disease: 'renal failure', 'kidney failure', 'renal impairment', 'kidney impairment', 'renal disease', 'kidney disease', 'ckd', 'dialysis', 'kidney transplant', 'renal transplant', 'kidney recipient', 'polycystic kidney', 'glomeruloneph', 'glomerulosclerosis', 'glomerular', 'nephritic', 'nephrotic', 'nephropathy', 'dysplasia', 'dysplastic', 'uropathy', 'tubular'. Common code stems were used to identify additional relevant codes. Codes referring specifically to acute conditions were excluded. A total of 544 relevant codes were identified (see appendix G.5).

The following truncated search terms were used to identify Read codes related to conditions associated with gastrointestinal malabsorption: 'malabsorption', 'cystic fibrosis', 'crohn', 'inflammatory bowel', 'ibd', 'ulcerative colitis', 'coeliac', 'celiac', 'short bowel', 'short gut', 'parenteral nutrition', 'pancreatic insufficiency', 'chronic pancreatitis', 'shwachman'. Common code stems were used to identify additional relevant codes. A total of 113 relevant codes were identified (see appendix G.6).

#### *5.3.6.9 Identification of Read Codes for Symptoms Related to Vitamin D Deficiency in Children*

A list of symptoms and clinical complications that can be caused by, although are not exclusive to, vitamin D deficiency in childhood was developed using information from

relevant review articles, guidelines, and case series (Ahmed et al, 2011; Callaghan et al, 2006; El-Fakhri et al, 2013; Ladhani et al, 2004; Misra et al, 2008; Munns et al, 2016; Pearce & Cheetham, 2010; RCPCH, 2013; Shaw & Mughal, 2013a; b; Ward et al, 2007; Wheeler et al, 2015). These were then grouped into 12 categories (see Table 5.5). The search terms used to identify Read codes related to each symptom group, and the final list of included codes for each category, are detailed in appendix G.7.

**Table 5.5** Grouping of symptoms and clinical complications related to vitamin D deficiency in children.

| Symptom Groups |
|---|
| Musculoskeletal and non-specific pain |
| Tiredness and fatigue |
| Skeletal deformity |
| Bone fracture |
| Failure to thrive |
| Hypocalcaemia |
| Seizure or tetany |
| Numbness or paraesthesia |
| Abnormal gait |
| Muscle weakness |
| Delay in motor development |
| Cardiomyopathy |

### *5.3.7 Data Management*

#### *5.3.7.1 Calculation of Prescribed Dosage*

Records of medication prescriptions in the THIN database contain information regarding the generic name and strength of the drug prescribed (through the drug code), as well as information regarding the dosage instruction specified by the prescriber. The 25,000 most commonly recorded dosage instructions in the database have been manually checked for removal of any patient identifiable data by IMS Health staff, and are provided in free text form in the dataset. Other dosage instructions are not routinely available to researchers, although they can be made available in anonymised form by IMS Health on request, for a fee, following manual review of the instruction free text and removal of any confidential information by IMS Health staff.

The code descriptions for each of the 246 drug codes related to pure preparations of calciferol were reviewed, and values for variables referring to the form of the unit of dosage (e.g. tablets or millilitres), and the unit strength of the drug in terms of international units (IU) of calciferol per dosage unit (i.e. IU per tablet, or IU per ml) were derived (see appendix G.1).

A total of 16,998 prescriptions of calciferol were identified in the study population during the study observation period. These prescriptions were linked to 5,114 unique dosage instructions, of which 874 were already available in the THIN dataset, whilst the remaining 4,240 were purchased from IMS Health following anonymisation. The free text for each of the 5,114 dosage instructions were manually reviewed, and values for the following variables were derived:

i) The form of the unit of dosage (e.g. tablets or millilitres), if specified.

ii) The time interval between the administration of each dose, in hours.

iii) The number of dosage units (e.g. tablets or millilitres) to be taken at the administration of each dose.

iv) The number of dosage units to be taken each day. For dosage instructions indicating administration at less frequently than daily intervals (e.g. weekly), this variable represents the equivalent number of dosage units for each 24-hour period.

v) The duration of the treatment in days, if specified.

vi) The total number of dosage units to be taken over the duration of the treatment, calculated if the duration of treatment was specified as less than 1 month.

vii) The number of IU of calciferol to be taken each day, if specified in the dosage instruction. For dosage instructions indicating administration at less frequently than daily intervals (e.g. weekly), this variable represents the equivalent number of IU of calciferol for each 24-hour period.

In the case of some dosage instructions, the prescribed dose was not clearly specified due to ambiguity in the instruction. In such cases, certain assumptions were made when coding the derived dosage variables. If the dosage instruction specified a range of possible doses rather than an exact dose, the mid-point of the range was taken. For example, for the instruction ‘TAKE 1 OR 2 DAILY’, the derived value for the number of

dosage units per day was 1.5. Some dosage instructions specified the frequency of administration, but did not indicate the number of dosage units to be taken at each administration time-point, e.g. 'TWICE A DAY'. In such cases, it was assumed that one dosage unit was taken at each administration time-point. Thus, the instruction 'TWICE A DAY' was assumed to represent '*ONE* TWICE A DAY'. This assumption was considered more likely to underestimate, rather than overestimate, the true prescribed dose. Making these assumptions was considered preferable to treating ambiguous dosage instructions as having missing data for the derived dosage variables, which would be likely to result in a greater degree of misclassification of cases as non-cases. A number of dosage instructions did not contain sufficient information from which to derive values for any of the dosage variables, e.g. 'USE AS DIRECTED', and in these cases the dosage was coded as missing. A selection of example dosage instructions, and the derived variables coded from the instruction text, are shown in Table 5.6.

The prescribed daily dose of calciferol in international units was calculated for each prescription by multiplying the unit strength of the preparation prescribed (derived from the drug code) by the number of dosage units to be taken each day (derived from the dosage instruction). Where the dosage instruction text also directly specified the dose in terms of IU of calciferol, this was given priority over the calculated daily dose if there was discrepancy between the two values.

For the main analyses, dosage instructions that specified a treatment duration of ≤14 days were considered to represent stoss (one-off) therapy. In these cases, instead of calculating the prescribed daily dose, the total dose of calciferol prescribed over the treatment period was calculated. A sensitivity analysis was performed to explore the influence of varying the choice of treatment duration considered to represent stoss therapy, from ≤7 days to <28 days.

It was possible to derive the prescribed dosage for 16,591 out of the total of 16,998 prescriptions of calciferol (97.6%). Dosage information was missing for 407 prescriptions (2.4%). For 1,303 of the prescriptions where the dosage could be derived (7.9%), the dosage instruction was not exact and an assumption was made regarding the number of dosage units to be taken at each administration time point.

**Table 5.6** Examples of dosage instructions and derived dosage variables.[a]

| Dosage instruction | Dosage unit | Time between doses (hours) | Dosage units per administration | Dosage units per day | Treatment duration (days) | Total dosage units, if duration <1 month | IU of calciferol per day |
|---|---|---|---|---|---|---|---|
| 1 TAB DAILY | tablet / capsule | 24 | 1 | 1 | - | - | - |
| 2MLS TWICE A DAY | ml | 12 | 2 | 4 | - | - | - |
| ONE ALTERNATE DAYS | - | 48 | 1 | 0.5 | - | - | - |
| 1 WEEKLY | - | 168 | 1 | 0.14286 | - | - | - |
| ONE MONTHLY | - | 672 | 1 | 0.0357 | - | - | - |
| 0.5MLS IMMEDIATELY | ml | - | 0.5 | - | 1 | 0.5 | - |
| 2 DAILY FOR 4 DAYS | - | 24 | 2 | 2 | 4 | 8 | - |
| 2ML (6000 UNITS) ONCE DAILY | ml | 24 | 2 | 2 | - | - | 6,000 |
| TAKE 1 OR 2 DAILY | - | 24 | 1.5 | 1.5 | - | - | - |
| TWICE A DAY | - | 12 | 1 | 2 | - | - | - |
| USE AS DIRECTED | - | - | - | - | - | - | - |

Abbreviation: IU, international units.

[a] Key variables for the calculation of prescribed dose are highlighted in yellow.

### 5.3.7.2 Data Cleaning for Vitamin D Test Results

The majority (90%) of vitamin D test results identified in the study population were recorded with the unit of measurement nmol/l, whilst the remaining 10% were recorded in ng/ml. As nmol/l is the usual unit of measurement for 25-OH-D in the UK, test results recorded in ng/ml were converted to nmol/l by multiplying the result value by a factor of 2.5 (SACN, 2016).

Read codes related to vitamin D tests (see section 5.3.6.5) were grouped into 4 categories based on the form of vitamin D specified by the code description (Table 5.7).

**Table 5.7** Categories of vitamin D test codes.

| Test category | Read code | Code description |
|---|---|---|
| Total 25-hydroxyvitamin D2 and D3 | 4QB4400 | Combined total vitamin D2 and D3 level |
| | 4QB4600 | Total 25-hydroxyvitamin D level |
| | 4QB4700 | Serum total 25-hydroxy vitamin D level |
| 25-hydroxyvitamin D3 | 44LM.00 | Plasma 25-Hydroxyvitamin D3 level |
| | 44LP.00 | Serum 25-Hydroxy vitamin D3 level |
| | 4QB4100 | Vitamin D3 level |
| | 4QB4300 | 25-Hydroxyvitamin D3 level |
| 25-hydroxyvitamin D2 | 44Lg.00 | Serum vitamin D2 level |
| | 44Ln.00 | Serum 25-Hydroxyvitamin D2 level |
| | 4QB4000 | Vitamin D2 level |
| | 4QB4200 | 25-Hydroxyvitamin D2 level |
| Unspecified vitamin D test | 44LA.00 | Serum vitamin D |
| | 4QB4.00 | Vitamin D level |
| | 4QB4500 | 25-Hydroxyvitamin D level |
| | 5788.00 | Radiobioassay - vitamin D[a] |

[a] There were no records for this code in the study cohort.

The distribution of test values for vitamin D tests identified in the study population were compared across each of the test categories (Table 5.8). The distribution of test values for the unspecified vitamin D tests was similar to that for vitamin D3 tests and total vitamin D2 & D3 tests. Therefore, unspecified vitamin D tests were considered to represent measurement of either 25-hydroxyvitamin D3 or total 25-hydroxyvitamin D2 & D3.

**Table 5.8** Distribution of test values across the vitamin D test categories.

| Test category | No. of tests | Distribution of test values in nmol/l Median (IQR) [1st–99th centiles] |
|---|---|---|
| Total vitamin D2 & D3 | 8,503 | 38 (22–59) [6.0–139] |
| Vitamin D3 | 20,178 | 35 (20–57) [5.0–144] |
| Vitamin D2 | 12,421 | 2.8 (1.0–5.0) [0.0–54] |
| Unspecified vitamin D | 43,698 | 37 (22–59) [7.0–147] |

Abbreviation: IQR, interquartile range.

Where a separate vitamin D2 and vitamin D3 test were recorded on the same date, the sum of the test results was calculated to give the total vitamin D2 & D3. Vitamin D test records were considered to represent vitamin D deficiency, and meet the case definition for the outcome, if there was a record of either a total vitamin D2 & D3, a vitamin D3, or an unspecified vitamin D test result with a value of <25 nmol/L.

#### *5.3.7.3 Data Cleaning for Ethnicity Records*

The consistency of ethnicity data within patient records has been shown to be higher in primary care electronic health data than in HES (Mathur et al, 2014). Therefore, for children with data available from both THIN and HES, ethnicity was assigned using THIN data. THIN Read codes referring directly to ethnicity, nationality or race were given precedence over codes referring to country of birth or language. Among children in the study cohort with ethnicity data available, final ethnicity was derived from codes referring directly to ethnicity, nationality or race for 99.5%, and from codes referring to country of birth or language in the remaining 0.5%.

In order to minimise conflicting ethnicity data within individual patients' records, a group of Read codes were identified which are less specific than others in their description of ethnicity, and which commonly caused conflict with other ethnicity records in the study population (Table 5.9).

**Table 5.9** Read codes that have a non-specific description of ethnicity.

| Read code | Description |
|---|---|
| 9SA..00 | Other ethnic non-mixed (NMO) |
| 9SAD.00 | Other ethnic NEC (NMO) |
| 9SJ..00 | Other ethnic group |
| 9iF..00 | Other - ethnic category 2001 census |
| 9iFK.00 | Any other group - ethnic category 2001 census |
| 9i0..00 | British or mixed British - ethnic category 2001 census |

All other ethnicity related Read codes were given precedence over these codes. For example, for a child with two ethnicity records, one for 'Other ethnic group' and the other for 'Indian', final ethnicity was coded as Indian. Similarly, for a child with an ethnicity record for 'British or mixed British - ethnic category 2001 census' as well as a record for 'Black British - ethnic category 2001 census', final ethnicity was coded as Black British.

Another common cause of conflict within individuals' ethnicity records was the combination of a code referring to 'other Asian' background (coded as 'Asian or Asian British' using the ONS 2001 Census 5-level classification), and a code referring to a Far Eastern, Middle Eastern or Arab background (which are all coded as 'Chinese or Other Ethnic Groups' using the ONS 2001 Census 5-level classification). Read codes referring to a non-specific Asian background are shown in Table 5.10.

**Table 5.10** Read codes referring to a non-specific Asian background.

| Read code | Description |
|---|---|
| 1343.00 | Asian origin |
| 2263.11 | O/E - Asian origin |
| 9SA8.00 | Other Asian (NMO) |
| 9SH.00 | Other Asian ethnic group |
| 9T1E.00 | Other Asian |
| 9iA.00 | Other Asian background - ethnic category 2001 census |
| 9iAA.00 | Other Asian or Asian unspecified ethnic category 2001 |

All codes assigned a 5-category ethnic group of 'Chinese or Other Ethnic Groups' were given precedence over the codes referring to a non-specific Asian background shown in Table 5.10. For example, for a child with an ethnicity record for 'Other Asian ethnic group' as well as a record for 'RACE: Korean', final ethnicity was coded as 'Chinese or Other Ethnic Groups'.

Following all of the above data management steps, among children with ethnicity data available, the proportion who had multiple ethnicity records belonging to different 5-level categories across THIN and HES was reduced from 5.5% to 0.5%. Among remaining children with ethnicity records belonging to more than one 5-level category, the most frequently recorded category was used. Where clashing ethnicity codes were recorded with the same frequency, ethnicity was coded as missing.

For children with no ethnicity data available, maternal ethnicity was used as a proxy measure for the child's ethnicity where it was available. The procedure for linking children to mothers in the THIN dataset is explained in section 5.3.7.4. Among children who had an ethnicity record available both for themselves as well as their linked mother, the two records matched at the 5-level ethnicity classification in 94% of cases.

#### *5.3.7.4 Linkage of Children to Mothers*

Children in the study cohort were linked to their mothers' in order to obtain information regarding maternal ethnicity, which was used as a proxy measure for children's ethnicity where this was missing (see section 5.3.5.2). A procedure for child-to-mother linkage was developed which was closely related to methods that have previously been used to link a cohort of pregnant women in THIN to their children (Petersen et al, 2016a). In summary, children in the study cohort were linked to women registered with the same general practice and sharing an identical 'household' identifier (see section 5.3.2.1), whose year of birth was between 14 to 50 years before the child's year of birth, and who had a record of pregnancy or delivery in their medical record where the expected, recorded, or predicted date of delivery was in proximity to the child's month of birth (or year of birth for older children age ≥15 years at February 2015).

Pregnancy or delivery related data is often recorded in the THIN database in the additional health data (AHD) file, using a separate group of codes called AHD codes. This allows additional data fields to be recorded, specific to each AHD code, such as the estimated date of delivery (EDD) or date of the last menstrual period (LMP). All AHD codes were manually reviewed (n=544), and those that are related to pregnancy or delivery were identified (Table 5.11). In addition to the AHD records, pregnancy and delivery records were also identified using relevant Read codes in patients' medical records (see section 5.3.6.7). Relevant Read codes were grouped into 19 categories, each referring to a common theme (Table 5.12) (see appendix G.3).

**Table 5.11** AHD codes related to pregnancy or delivery.

| AHD code | Description |
|---|---|
| 1001400092 | Pregnancy test [a] |
| 1001400161 | Maternity ultra sound scan |
| 1001400306 | Ante natal blood tests |
| 1009800000 | CHS – APGAR Score At 1 Minute |
| 1009810000 | CHS – APGAR Score At 5 Minutes |
| 1015000000 | Maternity outcome [b] |
| 1040000000 | Ante natal booking |
| 1041000000 | Ante natal consultation |
| 1044000000 | Postnatal examination |
| 1044100000 | Postnatal visit |
| 1046100000 | Ante natal fetal examination |
| 1047000000 | Maternity outcome gestational age of baby |
| 1048000000 | Maternity pregnancy dates – event date = LMP date |
| 1048100000 | Maternity delivery details baby [b] |
| 1048200000 | Maternity placenta |
| 1049000000 | CHS – gestation |
| 1050300000 | Maternity feeding |
| 1052500000 | Maternity infant details [b] |
| 1055400000 | Maternity perineum |
| 1055405000 | Maternity care plan |
| 1055500000 | CHS – delivery details [b] |
| 1055520000 | Maternity stages of labour |

[a] Only included in linkage if the test was specified as being positive.
[b] Not included in linkage if the outcome was specified as being a stillbirth, miscarriage, or neonatal death.

**Table 5.12** Categories of Read codes related to pregnancy or delivery.

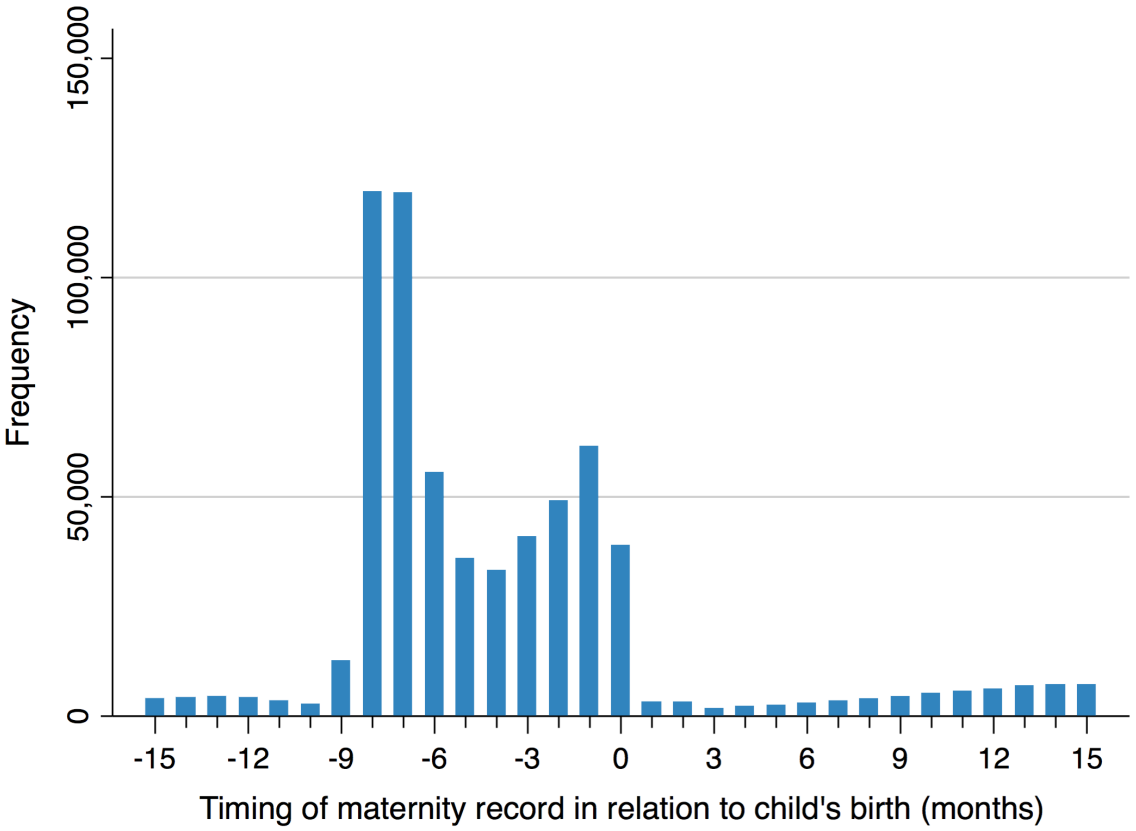
| Category |
|---|
| Pregnant |
| Pregnancy Test |
| Antenatal ultrasound scan |
| Antenatal examination |
| Antenatal care |
| Antenatal screening or test |
| Delivery booking |
| Estimated delivery date |
| Amniocentesis |
| Birth or delivery |
| Length of labour |
| Mode of birth |
| Sex of baby |
| Gestational age |
| Postnatal visit |
| Postnatal care |
| Postnatal examination |
| Hearing screen |
| Newborn registration |

Proximity rules for considering there to be a match between children's birth records and maternal pregnancy or delivery records were derived separately for each AHD code and each Read code group. Children in the study cohort were first linked to all women meeting each of the following criteria:

- Registered with the same general practice as the child.
- Recorded as having an acceptable patient record status (Patflag A or C).
- Period of active registration with the practice overlapping that of the child.
- Sharing an identical 'household' identifier with the child.
- Year of birth between 14 to 50 years before the child's year of birth.
- Recorded to have any pregnancy or delivery related AHD code or Read code in their patient record.

For each linked pair, the difference in time (in months) between the child's month of birth and the date of each maternal pregnancy or delivery record was calculated. The distribution of time differences between the children's birth records and maternal pregnancy / delivery records was explored, for each AHD code and each Read code group separately, to identify the period of proximity in which there was an increase or spike in frequency of records. This period was then used to derive proximity rules for considering the children's and maternal records to be a match, specific to each AHD code and Read code group. For example, for the AHD code for 'Maternity care plan' (1055405000), the frequency of records was above baseline in the period between 0 to 9 months before the children's month of birth (Figure 5.2). Therefore, where this code was recorded between 0 to 9 months before a child's month of birth, it was considered to represent a match between mother and child.

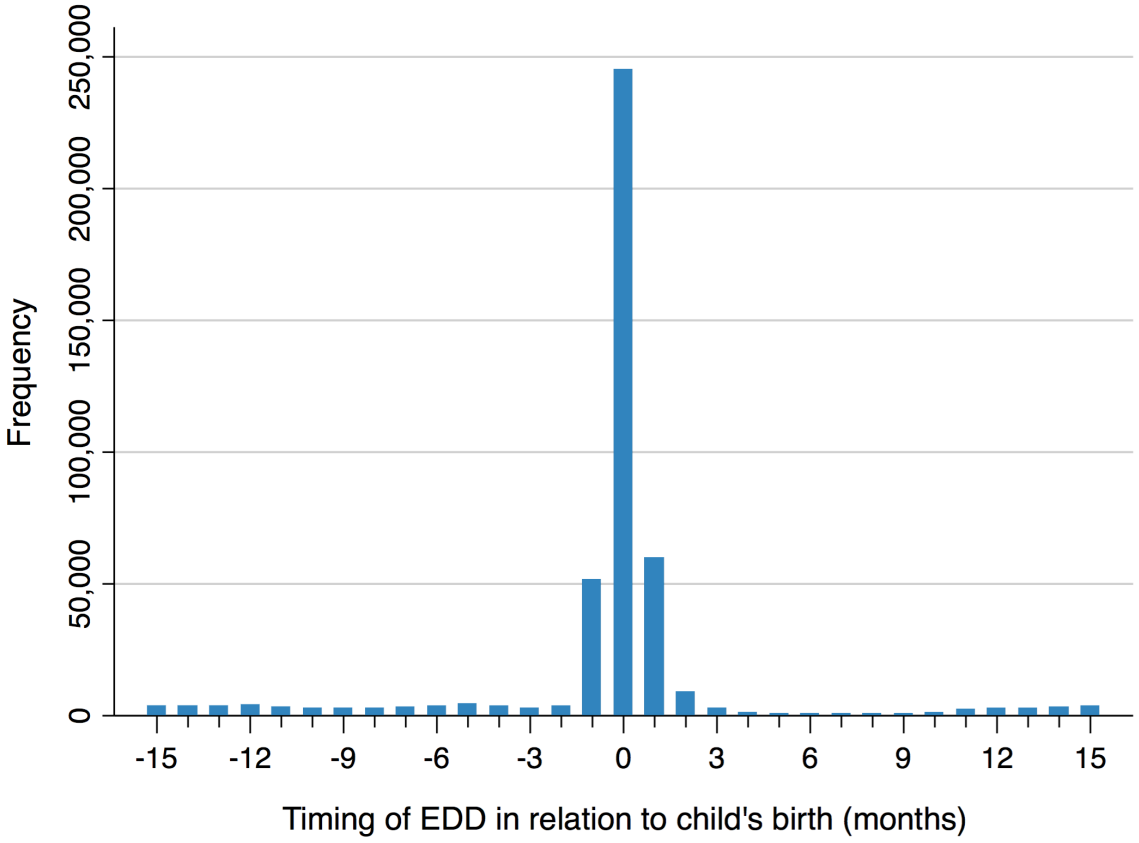
**Figure 5.2** Distribution of the timing of maternal records for the 'Maternity care plan' AHD code in relation to children's month of birth.[a]




[a] Graph limited to the period 15 months either side of children's month of birth, for purposes of clarity. This analysis includes all records for the AHD code 1055405000 ('Maternity care plan') in women in THIN, where women are registered with the same practice and share an identical 'household' identifier with a child in the study cohort, and where the woman's year of birth is between 14 to 50 years before the child's year of birth (n=655,540).

For AHD records providing information regarding the EDD or actual date of delivery, or other data from which the EDD could be calculated (such as the date of the LMP), the difference between the child's month of birth and the EDD or actual delivery date was calculated. Where the date of the LMP was given, the EDD was calculated as 280 days after the date of the LMP (ACOG, 2014). The distribution of time differences between the children's month of birth and the EDD or actual delivery dates was explored, and the period of proximity in which there was an increase in frequency of records was identified. For example, for the AHD code for 'Maternity pregnancy dates – event date = LMP date' (1048000000), the frequency of records demonstrated a spike where the EDD was between 1 month before to 1 month after the children's month of birth (Figure 5.3). Therefore, where this code was recorded with an EDD 1 month either side of a child's month of birth, it was considered to represent a match between mother and child.

**Figure 5.3** Distribution of the timing of estimated delivery dates (EDD) in relation to children's month of birth, for records of the AHD code 'Maternity pregnancy dates – event date = LMP date'.[a]




[a] Graph limited to the period 15 months either side of children's month of birth, for purposes of clarity. This analysis includes all records for the AHD code 1048000000 ('Maternity pregnancy dates – event date = LMP date') in women in THIN, where women are registered with the same practice and share an identical 'household' identifier with a child in the study cohort, and where the woman's year of birth is between 14 to 50 years before the child's year of birth (n=968,006).

For children age ≥15 years at February 2015, for whom only year of birth was available, maternity records where the EDD or actual date of delivery were in the same year as the child's year of birth were considered to represent a match between mother and child. For maternity records where the EDD or actual date of delivery were not given, the month of the maternity record was used to determine whether children born in the same year, previous year, or subsequent year were considered to represent a match. This decision was based upon the most common time at which each maternity related AHD code and Read code group was recorded in relation to the children's month of birth, determined using data from younger children for whom month of birth was available. For example, for the AHD code for 'Maternity care plan' (1055405000), there was a peak in frequency of records between 7 to 8 months before children's birth (Figure 5.2). Therefore, for older children for whom only year of birth was available,

where a maternity care plan was recorded between January to June, a child born in the same year was considered a match. However, for maternity care plans recorded between July to December, children born in the subsequent year were considered a match.

Proximity rules derived for child to mother linkage for each pregnancy or delivery related AHD code and Read code group are shown in appendix F.

Child to mother linkage was not performed for children with a 'household' identifier which was shared by a large number of people (≥20) during the period of the child's registration with the practice (1.1% of children in the study cohort). In such cases, the 'household' identifier was considered likely to represent a block of flats, and the risk of erroneous linkage was considered to be high. Linked mothers were excluded if children were matched to more than one potential mother (0.2% of children in the study cohort). Overall, 59.2% of children in the study cohort were successfully matched to a single mother.

### *5.3.8 Statistical Analysis*

All statistical and graphical analyses were performed using Stata MP version 14.2 (StataCorp, USA).

#### *5.3.8.1 Descriptive Analysis*

Descriptive characteristics of the study cohort were summarised using the numbers and percentages of individuals in each category for categorical variables, and using medians and interquartile ranges (IQR) for non-normally distributed continuous variables. Among children diagnosed with vitamin D deficiency, the frequency of recording of relevant symptom codes in the 6 months either side of the date of the first record meeting the case definition for the diagnosis of vitamin D deficiency was analysed. In addition, free text entries in the primary care medical record were purchased for a convenience sample of 55 children in the cohort with a diagnosis of vitamin D deficiency, in order to explore the extent to which free text could be used to obtain additional information regarding the presence of relevant symptoms. The convenience sample was chosen on the basis that free text dosage instructions were also being purchased for these children. All free text entries in the primary care medical

record in the 6 months either side of the date of the first record meeting the case definition for the diagnosis of vitamin D deficiency were examined. The free text provided additional information regarding symptoms related to vitamin D deficiency (Table 5.5), not already available from Read codes, in only 4 out of the 55 children (7.3%). Therefore, the purchase of further free text records for identification of symptoms among cases was not felt to be cost-efficient.

#### *5.3.8.2 Analysis of Time Trends in the Diagnosis of Vitamin D Deficiency*

Crude incidence rates for the diagnosis of vitamin D deficiency were calculated per 100,000 person-years at risk (PYAR), using the *stset and strate* functions in Stata. In order to explore incidence rates stratified by time-changing variables (age and calendar time), Lexis expansions were used to divide individuals' follow-up into distinct categories of the time-changing variables, using the *stsplit* function in Stata (Kirkwood & Sterne, 2003). Calendar time was split into individual years, between 2000 to 2014.

Plots of incidence rates for the diagnosis of vitamin D deficiency against time since registration with the general practice (Lewis plots) were used to explore whether there was evidence of greater recording of vitamin D deficiency diagnosis in the initial period after practice registration (Lewis et al, 2005).

#### *5.3.8.3 Crude Associations Between Study Covariates and Rates of Diagnosis of Vitamin D Deficiency*

Differences in rates of diagnosis of vitamin D deficiency by various socio-demographic factors were initially explored using rate ratios (RRs) to examine crude associations between incidence rates and each study covariate separately, using the *stmh* function in Stata. Significance tests were used to examine the null hypothesis that rate ratios were equal to 1.

#### *5.3.8.4 Multivariable Analyses*

Multivariable analyses were subsequently performed to examine adjusted associations between socio-demographic factors and incidence rates, taking into account the effect of all covariates simultaneously. For the multivariable analyses, the study cohort was limited to children registered with THIN practices that have linked HES data available

(the linked THIN-HES study cohort), in order to minimise missing data for ethnicity. Whilst ethnicity was available for only 48.1% of the full THIN study cohort, the addition of HES data substantially increased the availability of ethnicity data to 81.5% in the linked THIN-HES cohort (see section 5.4.2). The study period for the multivariable analyses was restricted to follow-up between 1st January 2008 and 31st December 2014, in view of the small numbers of cases (<30) of the outcome (diagnosis of vitamin D deficiency) in each year prior to 2008 (see section 5.4.3.9).

In the main multivariable analyses, Poisson regression was used to model rates of incident diagnosis of vitamin D deficiency whilst adjusting for sex, age group, ethnicity, Index of Multiple Deprivation (IMD), and calendar year (included as a categorical variable), using the *poisson* command in Stata. A sensitivity analysis was performed using the Townsend Index instead of the IMD, to explore the influence of the choice of measure of socio-economic position on the results. The IMD was used in subsequent analyses, on the basis that it is derived from a considerably broader range of indicator variables than the Townsend Index (see section 5.3.5.3).

Likelihood ratio tests (LRTs) were used to compare nested models with and without the inclusion of each covariate, to examine the null hypothesis of no overall association between each covariate and the rate of diagnosis of vitamin D deficiency. Evidence for interaction (effect modification) between explanatory variables in the model was investigated by examining the heterogeneity of stratum-specific rate ratios, and performing LRTs comparing the fit of models with and without the corresponding interaction terms. Evidence for interaction between covariates is presented graphically using plots of predicted margins (adjusted incidence rates predicted from Poisson regression models containing interaction terms) across the different categories of the relevant covariates (Williams, 2012). Interaction terms were retained in the final model if their inclusion resulted in both a qualitative change in parameter rate ratios and a significant LRT result ($p<0.05$).

#### *5.3.8.5 Multilevel Models*

The multivariable analysis was conducted with and without taking into account the clustered structure of the data. Initial model development and investigation of interaction was performed using single-level Poisson regression models, which did not account for data clustering. Multilevel Poisson regression models were developed to take into account the nested structure of the data. A two-level mixed-effects model was

developed with inclusion of the general practice as a random effect, using the *xtpoisson* command in Stata. A three-level mixed-effects model was also developed, additionally accounting for the nesting of practices within strategic health authority regions, using the *meqrpoisson* command in Stata.

#### *5.3.8.6 Methods for Handling Missing Data*

In the main multivariable analyses, missing data for model covariates was handled using complete cases analysis (listwise deletion). A sensitivity analysis was performed using multiple imputation of missing data, to explore the influence of the choice of method for handling missing data on the results. Data was incomplete for ethnicity and IMD, whilst complete data was available for the other model covariates (see section 5.4.2.2). Multivariable multiple imputation using chained equations was performed using the *mi impute chained* command in Stata (White et al, 2011). The imputation model included all variables in the substantive model, in addition to the following auxiliary variables which were shown to be associated with either ethnicity or IMD in the cohort:

- Year of birth, included as a continuous variable.
- Strategic health authority region.
- Townsend Index of deprivation.
- Ethnicity distribution of individuals sharing the same 'household' identifier. Separate categorical variables were created for each of the 5 ethnic groups, representing the proportion of individuals in the 'household' with the corresponding ethnicity (excluding individuals with missing data). Coded into 4 categories: 0, $0<x<0.5$, $0.5\leq x<1$, 1.
- Ethnicity distribution of individuals registered with the same general practice. Separate continuous variables were created for each of the 4 non-white ethnic groups, representing the proportion of the practice population with the corresponding ethnicity (excluding individuals with missing data). A variable for white ethnicity was not included, as inclusion of variables for all 5 ethnic groups resulted in collinearity (as their values always sum to 1).
- The mode (most common) IMD value among individuals sharing the same 'household' identifier.

- The IMD distribution among individuals registered with the same general practice. Four separate continuous variables were created for the IMD categories between 2 to 5, representing the proportion of the practice population with the corresponding IMD (excluding individuals with missing data). A variable for the IMD value of 1 was not included, as inclusion of variables for all 5 IMD categories resulted in collinearity (as their values always sum to 1).

The imputation model included any interaction terms present in the substantive model. Multinomial logistic regression was used for the conditional imputation model of ethnicity, whilst ordinal logistic regression was used for the conditional imputation model of IMD. Twenty imputed datasets were created.

### *5.3.9 Ethical Approval*

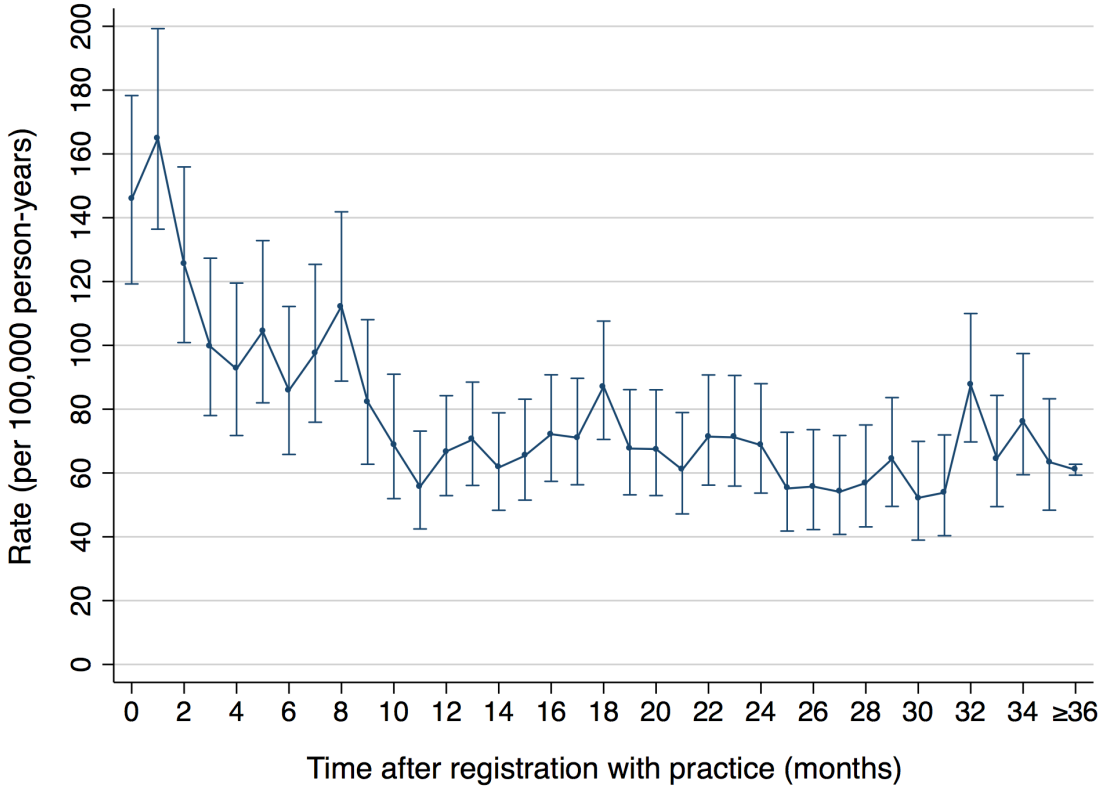
The THIN data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003 (http://www.epic-uk.org/our-data/ethics.shtml, accessed 22/10/2016). Under the terms of this approval, pre-collected, pseudo-anonymised patient data can be provided to researchers following independent scientific review, without the necessity for further approval from a Research Ethics Committee. Scientific approval for use of THIN data for this study was obtained from Cegedim Strategic Data Medical Research UK's Scientific Review Committee (reference 14–013, see appendix B.4).

## 5.4 Results

### *5.4.1 Relationship Between Time After Practice Registration and Rates of Diagnosis of Vitamin D Deficiency*

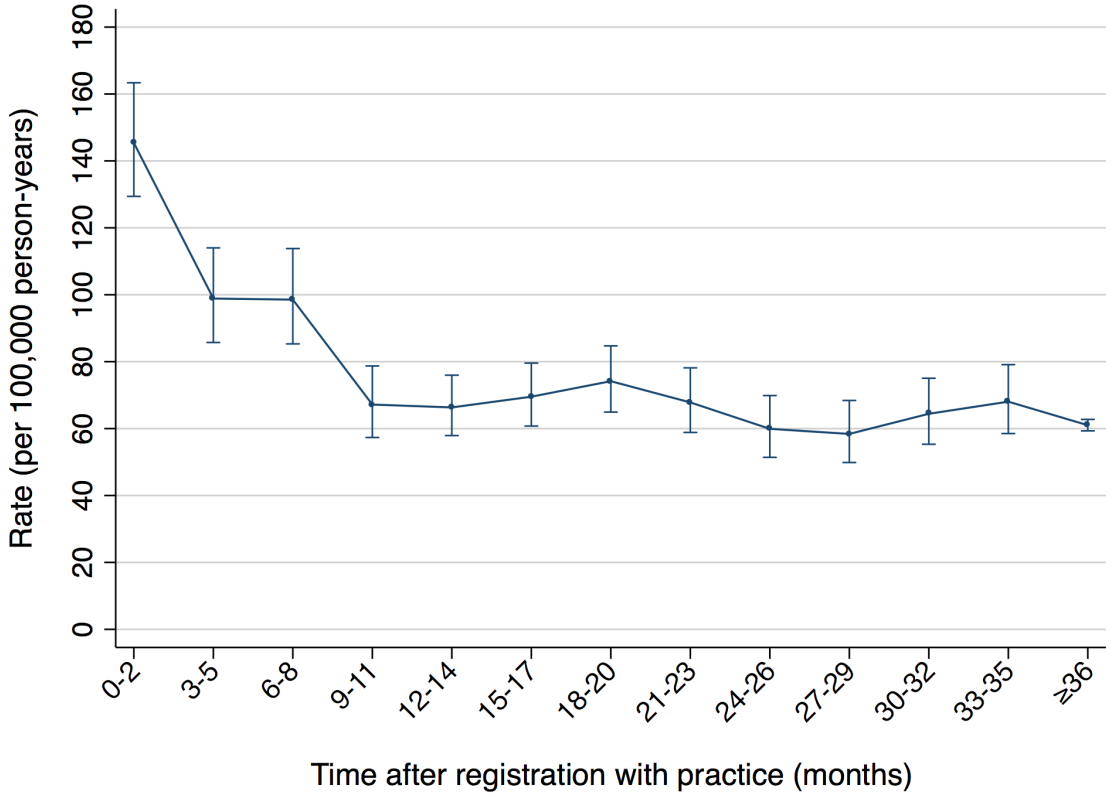
Plots of incidence rates for the diagnosis of vitamin D deficiency against time since registration with the general practice (Lewis plots) demonstrated that rates of recorded diagnosis were greatest in the first 3 months after registration, and reached baseline after 9 months following registration (Figures 5.4 and 5.5). In the main analyses, for children aged ≥1 year at the time of practice registration, the first 3 months after registration were excluded from follow-up. A sensitivity analysis was performed to explore the influence of varying this period of exclusion from between 0 to 9 months after practice registration. The period of exclusion was not necessary for infants under one year of age, for whom any recorded diagnoses can be considered incident (regardless of proximity to registration) as they will have occurred within the preceding year.

**Figure 5.4** Rates of diagnosis of vitamin D deficiency by time after registration with the general practice, in single month intervals.[a]




[a] Crude incidence rates are shown, with 95% confidence intervals represented by vertical lines.

**Figure 5.5** Rates of diagnosis of vitamin D deficiency by time after registration with the general practice, in 3 month intervals.[a]




[a] Crude incidence rates are shown, with 95% confidence intervals represented by vertical lines.

### *5.4.2 Descriptive Characteristics of the Study Cohort*

#### *5.4.2.1 Full THIN Study Cohort*

The full study cohort consisted of 2,338,529 children, from 639 general practices, with a total period of follow-up of 11.5 million person-years. Median duration of study follow-up was 3.7 years per individual (IQR 1.5 to 7.7). 11,913 children with a record of either chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption, were excluded from the study cohort. Descriptive characteristics of the study population are shown in Table 5.13. 7,297 children in the study cohort met the case definition for diagnosis of vitamin D deficiency during their period of follow-up.

In the full study cohort, information regarding ethnicity was derived from THIN primary care records only. Ethnicity was directly available for 40.1% of children in the cohort, and maternal ethnicity was available as a proxy measure of children's ethnicity for a

further 8.0% of the cohort. Ethnicity was missing for 51.9% of the study cohort. Townsend deprivation index was available for 93.8% of the cohort (missing for 6.2%).

**Table 5.13** Descriptive characteristics of the full study cohort (n=2,338,529).

| **Age at entry to follow-up (years)** | **Median (IQR)** |
|---|---|
| | 4.5 (0.42–10.7) |
| **Sex** | **n (%)** |
| Male | 1,205,379 (51.5%) |
| Female | 1,133,150 (48.5%) |
| **Ethnicity** [a] | **n (%)** |
| White | 939,886 (40.2%) |
| Asian or Asian British | 75,356 (3.2%) |
| Black or black British | 50,480 (2.2%) |
| Mixed | 30,795 (1.3%) |
| Chinese or other ethnic group | 29,141 (1.3%) |
| *Missing* | *1,212,871 (51.9%)* |
| **Townsend deprivation index quintile** | **n (%)** |
| 1 (least deprived) | 497,087 (21.3%) |
| 2 | 430,223 (18.4%) |
| 3 | 466,594 (20.0%) |
| 4 | 455,296 (19.5%) |
| 5 (most deprived) | 344,941 (14.8%) |
| *Missing* | *144,388 (6.2%)* |
| **Country, and strategic health authority in England** | **n (%)** |
| England | 1,828,119 (78.2%) |
| *South Central* | *269,240 (11.5%)* |
| *London* | *254,965 (10.9%)* |
| *South East Coast* | *211,205 (9.0%)* |
| *South West* | *208,298 (8.9%)* |
| *North West* | *199,913 (8.6%)* |
| *West Midlands* | *194,860 (8.3%)* |
| *East of England* | *153,355 (6.6%)* |
| *East Midlands* | *74,825 (3.2%)* |
| *Yorkshire & Humber* | *69,886 (3.0%)* |
| *North East* | *52,371 (2.2%)* |
| *Missing* | *139,201 (6.0%)* |
| Scotland | 269,606 (11.5%) |
| Wales | 164,380 (7.0%) |
| Northern Ireland | 76,424 (3.3%) |

Abbreviations: IQR, interquartile range.

[a] Ethnicity data was available from the child's THIN record for 40.1% of the cohort, and maternal ethnicity was available as a proxy measure for a further 8.0%.

#### 5.4.2.2 Study Cohort with Linked HES Data Available

When the analysis was limited to children registered with one of the 156 THIN practices in England for which linked HES data was available, the study cohort consisted of 711,788 children, with a total period of follow-up of 3.6 million person-years. Median duration of study follow-up was 3.9 years per individual (IQR 1.5 to 8.0). 3,916 children with a record of either chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption, were excluded from the study cohort. Descriptive characteristics of the linked THIN-HES study population are shown in Table 5.14. 2,918 children in the cohort met the case definition for diagnosis of vitamin D deficiency during their period of follow-up.

In the linked THIN-HES study cohort, information regarding ethnicity was derived from both THIN and HES records. Ethnicity was directly available for 67.7% of children in the cohort, and maternal ethnicity was available as a proxy measure of children's ethnicity for a further 13.8% of the cohort. Ethnicity was missing for 18.5% of the study cohort. Townsend deprivation index was available for 95.7% of the cohort (missing for 4.3%), and Index of Multiple Deprivation was available for 93.3% of the cohort (missing for 6.7%).

**Table 5.14** Descriptive characteristics of the THIN-HES linked study cohort (n=711,788).

| **Age at entry to follow-up (years)** | **Median (IQR)** |
|---|---|
| | 4.1 (0.40–10.5) |
| **Sex** | **n (%)** |
| Male | 366,378 (51.5%) |
| Female | 345,410 (48.5%) |
| **Ethnicity** [a] | **n (%)** |
| White | 491,962 (69.1%) |
| Asian or Asian British | 34,521 (4.9%) |
| Black or black British | 24,797 (3.5%) |
| Mixed | 15,558 (2.2%) |
| Chinese or other ethnic group | 13,443 (1.9%) |
| *Missing* | *131,507 (18.5%)* |
| **Townsend deprivation index quintile** | **n (%)** |
| 1 (least deprived) | 171,842 (24.1%) |
| 2 | 129,172 (18.2%) |
| 3 | 148,404 (20.9%) |
| 4 | 141,244 (19.8%) |
| 5 (most deprived) | 90,595 (12.7%) |
| *Missing* | *30,531 (4.3%)* |
| **Index of Multiple Deprivation quintile** | **n (%)** |
| 1 (least deprived) | 158,866 (22.3%) |
| 2 | 134,765 (18.9%) |
| 3 | 138,264 (19.4%) |
| 4 | 136,498 (19.2%) |
| 5 (most deprived) | 95,656 (13.4%) |
| *Missing* | *47,739 (6.7%)* |
| **Strategic health authority** | **n (%)** |
| South Central | 158,547 (22.3%) |
| South West | 111,817 (15.7%) |
| London | 100,718 (14.2%) |
| South East Coast | 91,619 (12.9%) |
| West Midlands | 89,796 (12.6%) |
| North West | 64,152 (9.0%) |
| East of England | 57,961 (8.1%) |
| North East | 18,532 (2.6%) |
| Yorkshire & Humber | 14,209 (2.0%) |
| East Midlands | 4,437 (0.6%) |

Abbreviations: IQR, interquartile range.

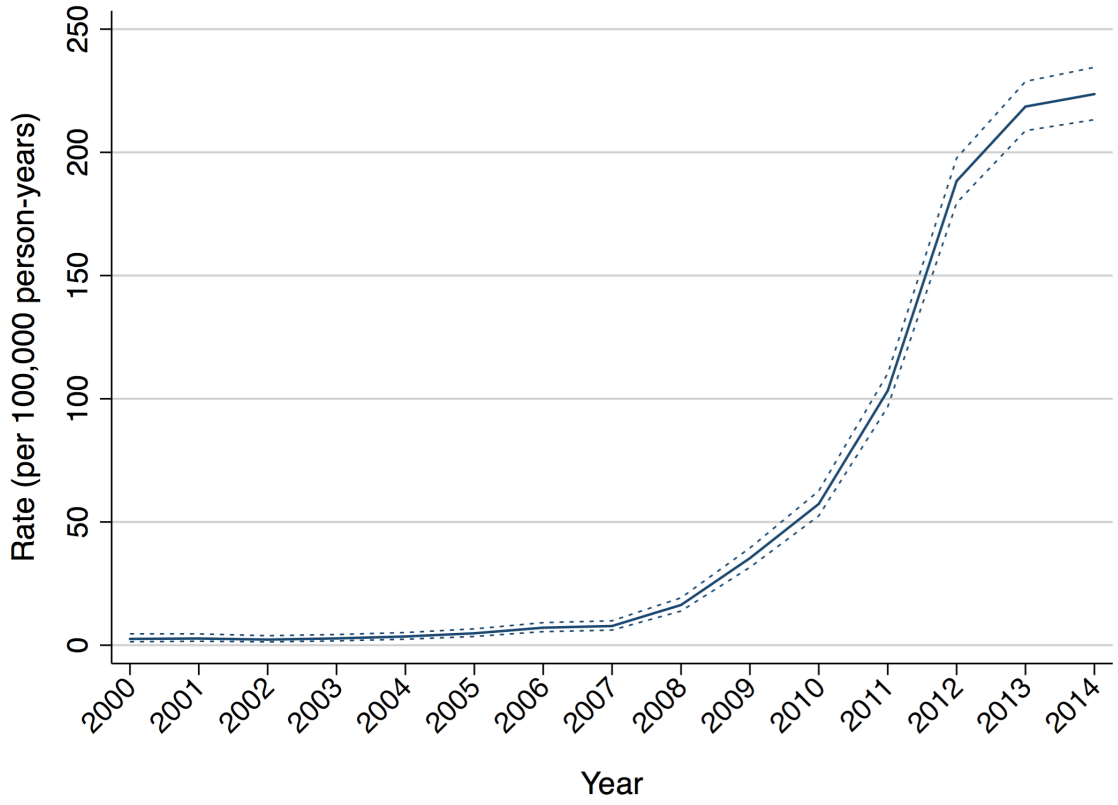
[a] Ethnicity data was available from the child's THIN or HES record for 67.7% of the cohort, and maternal ethnicity was available as a proxy measure for a further 13.8%.

### 5.4.3 Time Trends in the Diagnosis of Vitamin D Deficiency in Children

#### 5.4.3.1 Main Results Using the Full Study Cohort

Overall incidence rates for the diagnosis of vitamin D deficiency in the full THIN study cohort over time are shown in Figure 5.6 and Table 5.15. There was a marked increase in crude rates of diagnosis between 2008 to 2013, after which rates plateaued between 2013 to 2014.

**Figure 5.6** Time trends in the diagnosis of vitamin D deficiency in the full study cohort, between 2000 and 2014.[a]




[a] Crude incidence rates are shown, with 95% confidence limits represented by the dashed lines.

**Table 5.15** Crude incidence rates for the diagnosis of vitamin D deficiency in the full study cohort, by year between 2000 and 2014.

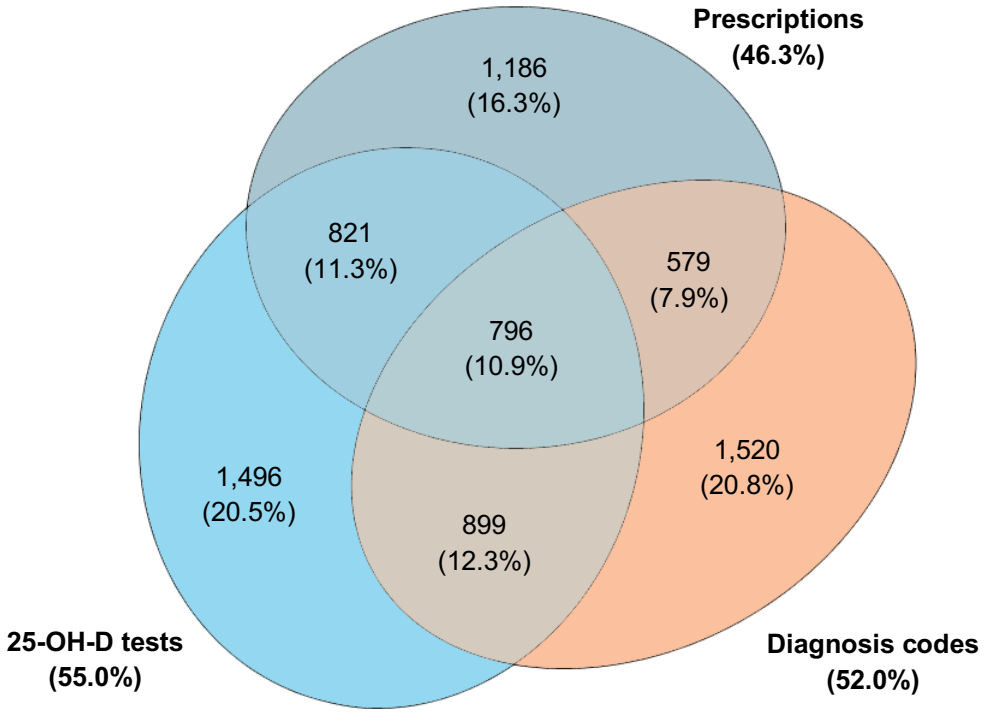
| Year | Number of cases | Person-years at risk (PYAR) | Incidence rate per 100,000 PYAR (95% CI) |
|---|---|---|---|
| 2000 | 11 | 430,721 | 2.55 (1.41–4.61) |
| 2001 | 14 | 515,596 | 2.72 (1.61–4.58) |
| 2002 | 14 | 614,946 | 2.28 (1.35–3.84) |
| 2003 | 19 | 688,371 | 2.76 (1.76–4.33) |
| 2004 | 27 | 766,064 | 3.52 (2.42–5.14) |
| 2005 | 39 | 805,582 | 4.84 (3.54–6.63) |
| 2006 | 59 | 831,792 | 7.09 (5.50–9.15) |
| 2007 | 67 | 860,350 | 7.79 (6.13–9.89) |
| 2008 | 143 | 875,935 | 16.3 (13.9–19.2) |
| 2009 | 312 | 883,603 | 35.3 (31.6–39.5) |
| 2010 | 496 | 865,219 | 57.3 (52.5–62.6) |
| 2011 | 901 | 872,353 | 103 (96.8–110) |
| 2012 | 1,652 | 877,054 | 188 (179–198) |
| 2013 | 1,839 | 841,381 | 219 (209–229) |
| 2014 | 1,704 | 761,971 | 224 (213–235) |

Abbreviations: CI, confidence interval; PYAR, person-years at risk.

### 5.4.3.2 Sources of Case Identification

Figure 5.7 shows the overlap between cases identified from diagnosis codes, prescription records, and 25-OH-D test records.

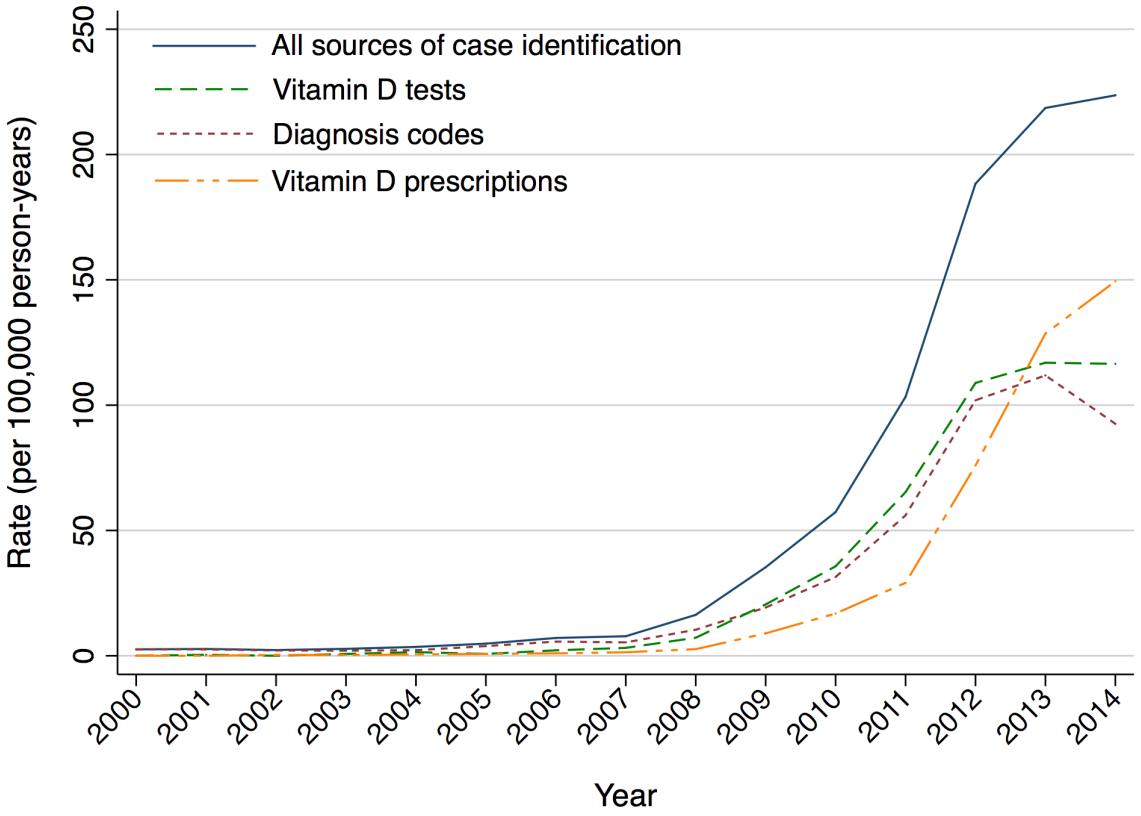
**Figure 5.7** Venn diagram showing the overlap between the sources of case identification.[a]




[a] The figures represent numbers of cases (percentages). N=7,297.

Considerably lower incidence rates were obtained when the three components of the case definition were examined independently rather than being used together (Figure 5.8 and Table 5.16). Similar trends over time were seen with each source of case identification.

**Figure 5.8** Time trends in incidence rates for the diagnosis of vitamin D deficiency, using all components of the case definition together and each source of case identification independently.[a]




[a] Crude incidence rates are shown between 2000 and 2014 in the full study cohort.

**Table 5.16** Crude incidence rates obtained using each component of the case definition for diagnosis of vitamin D deficiency separately, in each year between 2000 and 2014.[a]

| Year | Diagnosis Read codes | | Vitamin D prescription records | | 25-OH-D test records | |
|---|---|---|---|---|---|---|
| | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 2.55 (1.41–4.61) | 0 | 0 | 0 | 0 |
| 2001 | 13 | 2.52 (1.46–4.34) | 0 | 0 | 2 | 0.39 (0.10–1.55) |
| 2002 | 13 | 2.11 (1.23–3.64) | 2 | 0.33 (0.08–1.30) | 0 | 0 |
| 2003 | 14 | 2.03 (1.20–3.43) | 2 | 0.29 (0.07–1.16) | 5 | 0.73 (0.30–1.74) |
| 2004 | 17 | 2.22 (1.38–3.57) | 4 | 0.52 (0.20–1.39) | 11 | 1.44 (0.80–2.59) |
| 2005 | 31 | 3.85 (2.71–5.47) | 6 | 0.74 (0.33–1.66) | 6 | 0.74 (0.33–1.66) |
| 2006 | 47 | 5.65 (4.25–7.52) | 8 | 0.96 (0.48–1.92) | 18 | 2.16 (1.36–3.43) |
| 2007 | 46 | 5.35 (4.00–7.14) | 12 | 1.39 (0.79–2.46) | 27 | 3.14 (2.15–4.57) |
| 2008 | 91 | 10.4 (8.46–12.8) | 23 | 2.62 (1.74–3.95) | 63 | 7.19 (5.62–9.20) |
| 2009 | 170 | 19.2 (16.6–22.4) | 79 | 8.94 (7.17–11.1) | 181 | 20.5 (17.7–23.7) |
| 2010 | 272 | 31.4 (27.9–35.4) | 146 | 16.9 (14.3–19.8) | 309 | 35.7 (31.9–39.9) |
| 2011 | 489 | 56.0 (51.3–61.2) | 254 | 29.1 (25.7–32.9) | 570 | 65.3 (60.1–70.9) |
| 2012 | 895 | 102 (95.5–109) | 667 | 75.9 (70.4–81.9) | 956 | 109 (102–116) |
| 2013 | 943 | 112 (105–119) | 1,085 | 129 (121–136) | 986 | 117 (110–124) |
| 2014 | 707 | 92.6 (86.0–99.6) | 1,142 | 149 (141–158) | 890 | 116 (109–124) |

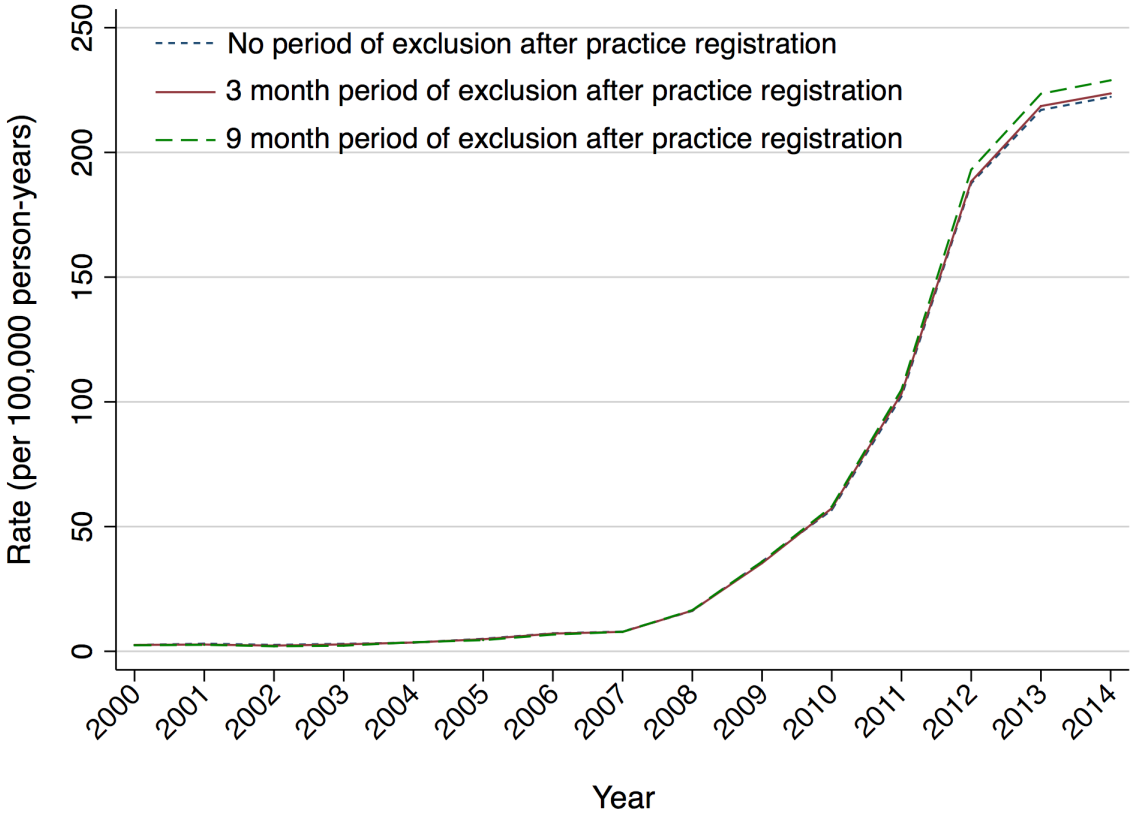
Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; PYAR, person-years at risk.

[a] The analysis used the full study cohort.

#### 5.4.3.3 *Sensitivity Analysis Exploring the Impact of Varying the Period of Exclusion from Follow-up after Practice Registration*

Observed rates of diagnosis of vitamin D deficiency did not differ substantially when the period of exclusion from follow-up following practice registration was varied between 0 to 9 months, for children aged ≥1 year at the time of practice registration (Figure 5.9 and Table 5.17).

**Figure 5.9** Time trends in the diagnosis of vitamin D deficiency, using varying periods of exclusion from follow-up after practice registration.[a]




[a] Crude incidence rates are shown between 2000 and 2014 in the full study cohort. For children aged ≥1 year at the time of practice registration, varying periods of time following practice registration were excluded from follow-up; no period of exclusion (dashed blue line), 3-month period of exclusion (solid red line), and 9-month period of exclusion (dashed green line). No period of exclusion was employed for infants under the age of one year at the time of practice registration.

**Table 5.17** Crude incidence rates for the diagnosis of vitamin D deficiency between 2000 and 2014, using varying periods of exclusion from follow-up after practice registration.[a]

| Year | No period of exclusion after registration | | 3-month period of exclusion after registration | | 9-month period of exclusion after registration | |
|---|---|---|---|---|---|---|
| | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 2.52 (1.39–4.54) | 11 | 2.55 (1.41–4.61) | 10 | 2.39 (1.29–4.45) |
| 2001 | 16 | 3.06 (1.87–4.99) | 14 | 2.72 (1.61–4.58) | 13 | 2.60 (1.51–4.47) |
| 2002 | 16 | 2.56 (1.57–4.19) | 14 | 2.28 (1.35–3.84) | 12 | 2.01 (1.14–3.54) |
| 2003 | 21 | 3.01 (1.96–4.61) | 19 | 2.76 (1.76–4.33) | 15 | 2.24 (1.35–3.72) |
| 2004 | 27 | 3.47 (2.38–5.06) | 27 | 3.52 (2.42–5.14) | 27 | 3.63 (2.49–5.30) |
| 2005 | 41 | 5.01 (3.69–6.81) | 39 | 4.84 (3.54–6.63) | 35 | 4.48 (3.22–6.24) |
| 2006 | 61 | 7.22 (5.62–9.28) | 59 | 7.09 (5.50–9.15) | 54 | 6.69 (5.13–8.74) |
| 2007 | 69 | 7.89 (6.24–10.0) | 67 | 7.79 (6.13–9.89) | 65 | 7.79 (6.11–9.94) |
| 2008 | 144 | 16.2 (13.7–19.0) | 143 | 16.3 (13.9–19.2) | 140 | 16.5 (14.0–19.5) |
| 2009 | 323 | 36.0 (32.3–40.1) | 312 | 35.3 (31.6–39.5) | 308 | 36.0 (32.2–40.2) |
| 2010 | 498 | 56.6 (51.9–61.8) | 496 | 57.3 (52.5–62.6) | 486 | 58.0 (53.1–63.4) |
| 2011 | 906 | 102.2 (95.8–109) | 901 | 103 (96.8–110) | 886 | 105 (98.2–112) |
| 2012 | 1,672 | 188 (179–197) | 1,652 | 188 (179–198) | 1,640 | 193 (184–203) |
| 2013 | 1,854 | 217 (207–227) | 1,839 | 219 (209–229) | 1,823 | 224 (213–234) |
| 2014 | 1,716 | 222 (212–233) | 1,704 | 224 (213–235) | 1,692 | 229 (218–240) |

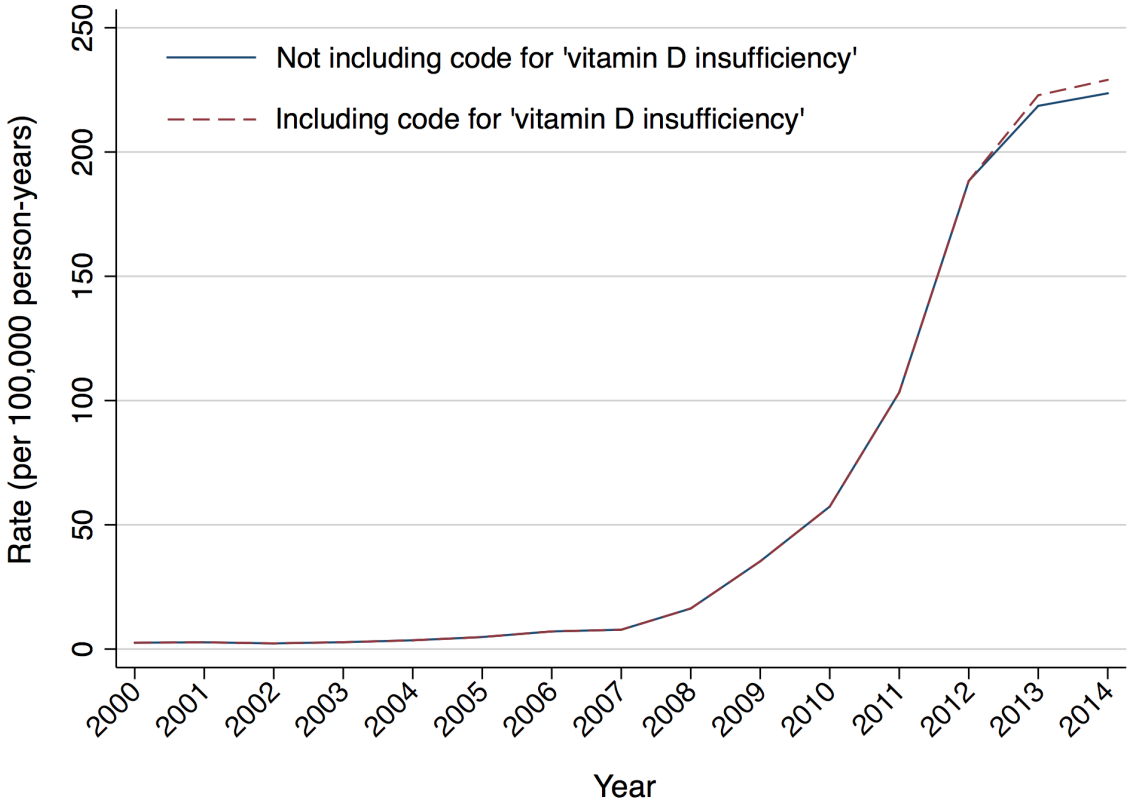
Abbreviations: CI, confidence interval; PYAR, person-years at risk.

[a] The analysis used the full study cohort. For children aged ≥1 year at the time of practice registration, varying periods of time following practice registration were excluded from follow-up; no period of exclusion, 3-month period of exclusion, and 9-month period of exclusion. No period of exclusion was employed for infants under the age of one year at the time of practice registration.

#### 5.4.3.4 *Sensitivity Analysis Exploring the Impact of Inclusion of the Read Code for 'Vitamin D insufficiency' in the Case Definition*

Observed rates of diagnosis of vitamin D deficiency did not differ substantially when the Read code for 'Vitamin D insufficiency' (C2B..00), which was added to the Read code dictionary in 2013, was included in the case definition (Figure 5.10 and Table 5.18).

**Figure 5.10** Time trends in the diagnosis of vitamin D deficiency, with and without inclusion of the Read code for 'Vitamin D insufficiency' in the case definition.[a]




[a] Crude incidence rates are shown between 2000 and 2014 in the full study cohort.

**Table 5.18** Crude incidence rates for the diagnosis of vitamin D deficiency between 2000 and 2014, with and without inclusion of the Read code for 'Vitamin D insufficiency' in the case definition.[a]

| Year | Not including Read code for 'Vitamin D Insufficiency' | | Including Read code for 'Vitamin D Insufficiency' | |
|---|---|---|---|---|
| | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 2.55 (1.41–4.61) | 11 | 2.55 (1.41–4.61) |
| 2001 | 14 | 2.72 (1.61–4.58) | 14 | 2.72 (1.61–4.58) |
| 2002 | 14 | 2.28 (1.35–3.84) | 14 | 2.28 (1.35–3.84) |
| 2003 | 19 | 2.76 (1.76–4.33) | 19 | 2.76 (1.76–4.33) |
| 2004 | 27 | 3.52 (2.42–5.14) | 27 | 3.52 (2.42–5.14) |
| 2005 | 39 | 4.84 (3.54–6.63) | 39 | 4.84 (3.54–6.63) |
| 2006 | 59 | 7.09 (5.50–9.15) | 59 | 7.09 (5.50–9.15) |
| 2007 | 67 | 7.79 (6.13–9.89) | 67 | 7.79 (6.13–9.89) |
| 2008 | 143 | 16.3 (13.9–19.2) | 143 | 16.3 (13.9–19.2) |
| 2009 | 312 | 35.3 (31.6–39.5) | 312 | 35.3 (31.6–39.5) |
| 2010 | 496 | 57.3 (52.5–62.6) | 496 | 57.3 (52.5–62.6) |
| 2011 | 901 | 103 (96.8–110) | 901 | 103 (96.8–110) |
| 2012 | 1,652 | 188 (179–198) | 1,652 | 188 (179–198) |
| 2013 | 1,839 | 219 (209–229) | 1,875 | 223 (213–233) |
| 2014 | 1,704 | 224 (213–235) | 1,745 | 229 (219–240) |

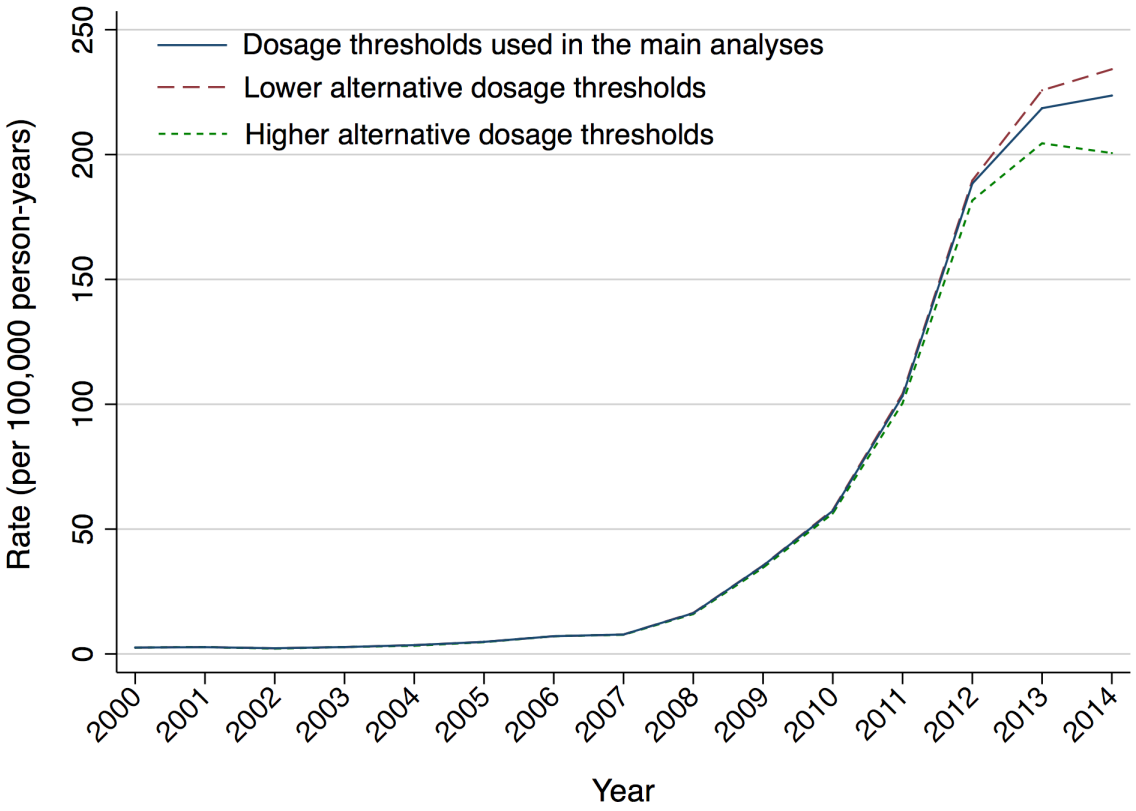
Abbreviations: CI, confidence interval; PYAR, person-years at risk.

[a] The analysis used the full study cohort.

#### 5.4.3.5 *Sensitivity Analysis Exploring the Impact of Using Different Dosage Thresholds for Calciferol Prescriptions in the Case Definition*

Observed rates of diagnosis of vitamin D deficiency prior to 2013 were very similar when a range of alternative dosage thresholds representing 'treatment dose' prescriptions of calciferol were used in the case definition (Figure 5.11 and Table 5.19). In 2013 and 2014, rates were somewhat lower when the higher alternative dosage thresholds (representing recommended treatment doses in the BNFc) were used. The maximal relative difference between rates obtained using the dosage thresholds used in the main analysis and the higher BNFc thresholds was 10.3%, in 2014.

**Figure 5.11** Time trends in the diagnosis of vitamin D deficiency, using alternative dosage thresholds to represent 'treatment dose' prescriptions of calciferol in the case definition.[a]




[a] Crude incidence rates are shown between 2000 and 2014 in the full study cohort. In the main analyses, 'treatment dose' of calciferol was defined as: ≥1,500 units/day if age <6 months, ≥3,000 units/day if age 6 months to 12 years, ≥5,000 units/day if age >12 years, or a one-off (stoss) dose of ≥100,000 units at any age (solid blue line). Using the lower alternative dosage thresholds, 'treatment dose' of calciferol was defined as: ≥1,000 units/day if age <6 months, ≥2,000 units/day if age 6 months to 12 years, ≥3,000 units/day if age >12 years, or a one-off dose of ≥100,000 units at any age (dashed red line). Using the higher alternative dosage thresholds, 'treatment dose' of calciferol was defined as: ≥3,000 units/day if age <6 months, ≥6,000 units/day if age 6 months to 12 years, ≥10,000 units/day if age >12 years, or a one-off dose of ≥100,000 units at any age (dashed green line).

**Table 5.19** Crude incidence rates for the diagnosis of vitamin D deficiency between 2000 and 2014, using alternative dosage thresholds to represent 'treatment dose' prescriptions of calciferol in the case definition.[a]

| Year | Dosage thresholds used in the main analyses [b] | | Lower alternative dosage thresholds [c] | | Higher alternative dosage thresholds [d] | |
|---|---|---|---|---|---|---|
| | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 2.55 (1.41–4.61) | 11 | 2.55 (1.41–4.61) | 11 | 2.55 (1.41–4.61) |
| 2001 | 14 | 2.72 (1.61–4.58) | 14 | 2.72 (1.61–4.58) | 14 | 2.72 (1.61–4.58) |
| 2002 | 14 | 2.28 (1.35–3.84) | 14 | 2.28 (1.35–3.84) | 13 | 2.11 (1.23–3.64) |
| 2003 | 19 | 2.76 (1.76–4.33) | 19 | 2.76 (1.76–4.33) | 19 | 2.76 (1.76–4.33) |
| 2004 | 27 | 3.52 (2.42–5.14) | 27 | 3.52 (2.42–5.14) | 25 | 3.26 (2.21–4.83) |
| 2005 | 39 | 4.84 (3.54–6.63) | 39 | 4.84 (3.54–6.63) | 38 | 4.72 (3.43–6.48) |
| 2006 | 59 | 7.09 (5.50–9.15) | 59 | 7.09 (5.50–9.15) | 59 | 7.09 (5.50–9.15) |
| 2007 | 67 | 7.79 (6.13–9.89) | 67 | 7.79 (6.13–9.89) | 66 | 7.67 (6.03–9.76) |
| 2008 | 143 | 16.3 (13.9–19.2) | 144 | 16.4 (14.0–19.4) | 140 | 16.0 (13.5–18.9) |
| 2009 | 312 | 35.3 (31.6–39.5) | 313 | 35.4 (31.7–39.6) | 305 | 34.5 (30.9–38.6) |
| 2010 | 496 | 57.3 (52.5–62.6) | 499 | 57.7 (52.8–63.0) | 487 | 56.3 (51.5–61.5) |
| 2011 | 901 | 103 (96.8–110) | 909 | 104 (97.6–111) | 876 | 100 (94.0–107) |
| 2012 | 1,652 | 188 (179–198) | 1,663 | 190 (181–199) | 1,593 | 182 (173–191) |
| 2013 | 1,839 | 219 (209–229) | 1,899 | 226 (216–236) | 1,721 | 205 (195–214) |
| 2014 | 1,704 | 224 (213–235) | 1,784 | 234 (224–245) | 1,529 | 201 (191–211) |

Abbreviations: CI, confidence interval; PYAR, person-years at risk.
[a] The analysis used the full study cohort.
[b] In the main analyses, 'treatment dose' of calciferol was defined as: ≥1,500 units/day if age <6 months, ≥3,000 units/day if age 6 months to 12 years, ≥5,000 units/day if age >12 years, or a one-off (stoss) dose of ≥100,000 units at any age.
[c] Using the lower alternative dosage thresholds, 'treatment dose' of calciferol was defined as: ≥1,000 units/day if age <6 months, ≥2,000 units/day if age 6 months to 12 years, ≥3,000 units/day if age >12 years, or a one-off dose of ≥100,000 units at any age.
[d] Using the higher alternative dosage thresholds, 'treatment dose' of calciferol was defined as: ≥3,000 units/day if age <6 months, ≥6,000 units/day if age 6 months to 12 years, ≥10,000 units/day if age >12 years, or a one-off dose of ≥100,000 units at any age.

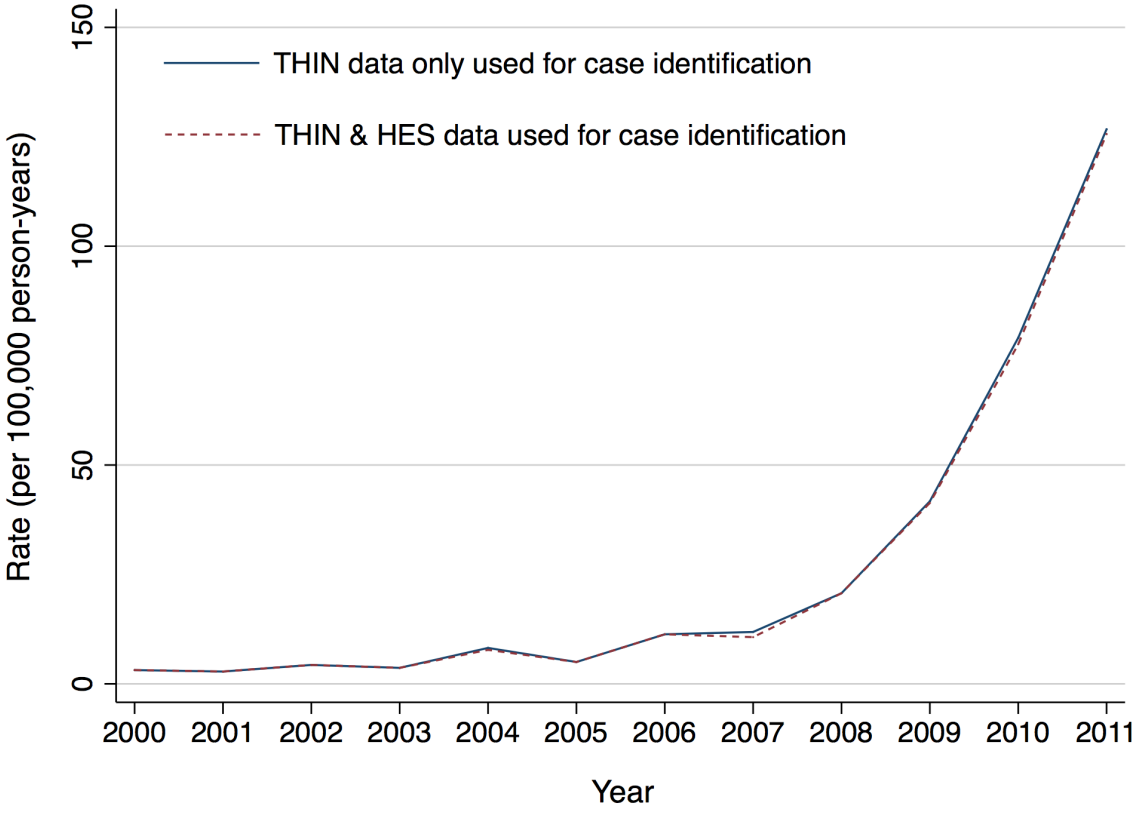
#### *5.4.3.6 Sensitivity Analysis Exploring the Impact of Varying the Duration of Treatment with Calciferol Considered to Represent One-Off (Stoss) Therapy*

Observed rates of diagnosis of vitamin D deficiency remained identical when the duration of treatment with calciferol considered to represent one-off (stoss) therapy was varied between ≤7 days to <28 days.

### 5.4.3.7 *Sensitivity Analysis Exploring the Impact of Inclusion ICD-10 Codes from HES Inpatient Records in the Case Definition*

Observed rates of diagnosis of vitamin D deficiency did not differ substantially when ICD-10 codes related to vitamin D deficiency or rickets, from HES inpatient records, were included in the case definition (Figure 5.12 and Table 5.20). The study population for this analysis was limited to individuals registered with THIN practices for which linked HES data was available. The time period for which linked HES data was available limited the study period for this analysis to follow-up between 1st January 2000 and 31st December 2011.

**Figure 5.12** Time trends in the diagnosis of vitamin D deficiency, with and without inclusion of ICD-10 codes related to vitamin D deficiency and rickets from HES inpatient records in the case definition.[a]




[a] Crude incidence rates are shown between 2000 and 2011 in the linked THIN-HES study cohort.

**Table 5.20** Crude incidence rates for the diagnosis of vitamin D deficiency between 2000 and 2011, with and without inclusion of ICD-10 codes related to vitamin D deficiency and rickets from HES inpatient records in the case definition.[a]

| Year | THIN data only used for case identification | | | HES inpatient records used as an additional source of case identification | | |
|---|---|---|---|---|---|---|
| | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 5 | 159,318 | 3.14 (1.31–7.54) | 5 | 159,318 | 3.14 (1.31–7.54) |
| 2001 | 5 | 177,945 | 2.81 (1.17–6.75) | 5 | 177,945 | 2.81 (1.17–6.75) |
| 2002 | 9 | 208,386 | 4.32 (2.25–8.30) | 9 | 208,386 | 4.32 (2.25–8.30) |
| 2003 | 8 | 219,036 | 3.65 (1.83–7.30) | 8 | 219,035 | 3.65 (1.83–7.30) |
| 2004 | 18 | 231,690 | 7.77 (4.89–12.3) | 19 | 231,687 | 8.20 (5.23–12.9) |
| 2005 | 12 | 240,543 | 4.99 (2.83–8.78) | 12 | 240,540 | 4.99 (2.83–8.78) |
| 2006 | 28 | 247,374 | 11.3 (7.82–16.4) | 28 | 247,367 | 11.3 (7.82–16.4) |
| 2007 | 27 | 253,053 | 10.7 (7.32–15.6) | 30 | 253,043 | 11.9 (8.29–17.0) |
| 2008 | 54 | 260,812 | 20.7 (15.9–27.0) | 54 | 260,798 | 20.7 (15.9–27.0) |
| 2009 | 110 | 266,102 | 41.3 (34.3–49.8) | 111 | 266,086 | 41.7 (34.6–50.2) |
| 2010 | 212 | 273,216 | 77.6 (67.8–88.8) | 216 | 273,190 | 79.1 (69.2–90.3) |
| 2011 | 351 | 279,387 | 126 (113–139) | 354 | 279,348 | 127 (114–141) |

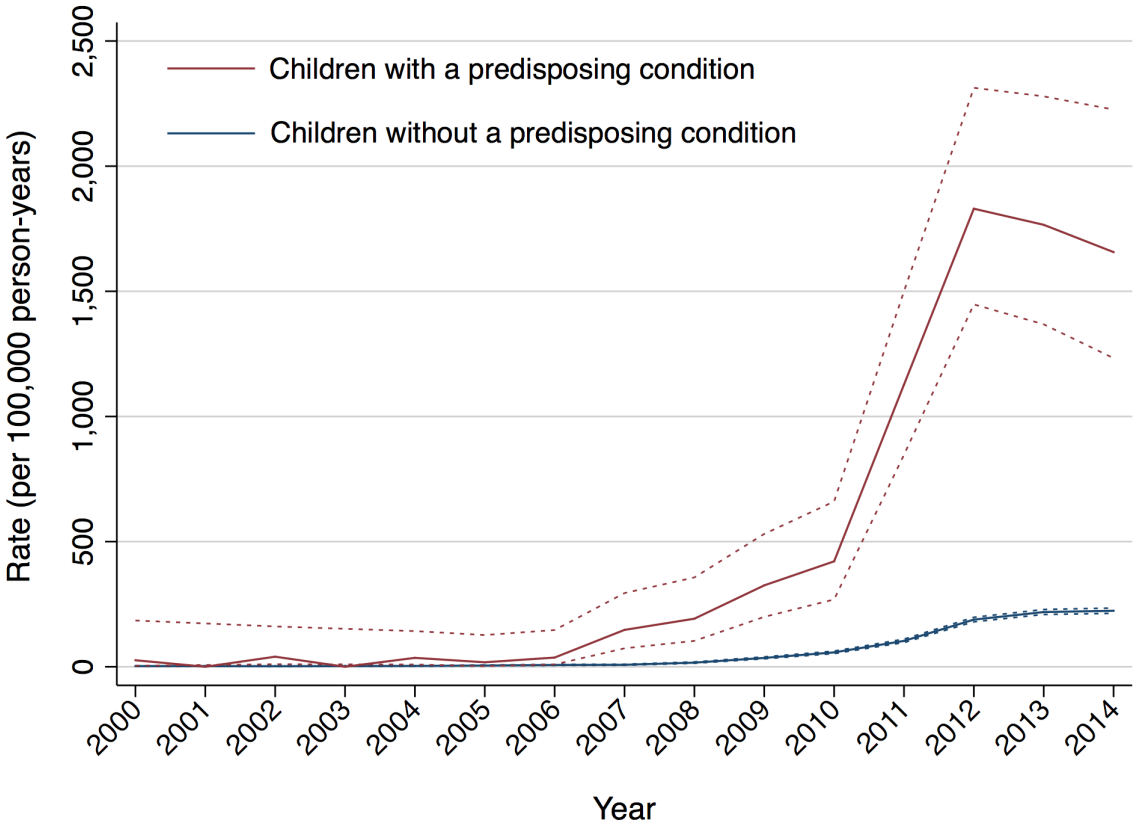
Abbreviations: CI, confidence interval; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases 10th edition; PYAR, person-years at risk; THIN, The Health Improvement Network.

[a] The analysis used the linked THIN-HES study cohort.

### 5.4.3.8 *Diagnosis of Vitamin D Deficiency Among Children with Medical Conditions that Interfere with Vitamin D Absorption or Metabolism*

In analysis including children with a record of a medical condition that can predispose to vitamin D deficiency by interfering with vitamin D absorption or metabolism (chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption), incidence rates for the diagnosis of vitamin D deficiency were considerably higher among children with a predisposing condition (Figure 5.13 and Table 5.21). Among children with predisposing conditions (n=11,913), observed diagnosis rates in the earlier years of the study period should be treated with caution in view of the small numbers of cases in each year (<10 per year prior to 2008).

**Figure 5.13** Time trends in the diagnosis of vitamin D deficiency, among children with and without predisposing medical conditions that can interfere with vitamin D absorption or metabolism.[a]




[a] Crude incidence rates are shown between 2000 and 2014 in the full study cohort, including children with a record of a medical condition that can predispose to vitamin D deficiency by interfering with vitamin D absorption or metabolism (chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption). The dashed lines represent 95% confidence limits.

**Table 5.21** Crude incidence rates for the diagnosis of vitamin D deficiency between 2000 and 2011, among children with and without predisposing medical conditions that can interfere with vitamin D absorption or metabolism.[a]

| Year | Children without chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption (n= 2,338,529) | | | Children with chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption (n=11,913) | | |
|---|---|---|---|---|---|---|
| | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 430,721 | 2.55 (1.41–4.61) | 1 | 3,843 | 26.0 (3.67–185) |
| 2001 | 14 | 515,596 | 2.72 (1.61–4.58) | 0 | 4,392 | 0 |
| 2002 | 14 | 614,946 | 2.28 (1.35–3.84) | 2 | 4,968 | 40.3 (10.1–161) |
| 2003 | 19 | 688,371 | 2.76 (1.76–4.33) | 0 | 5,324 | 0 |
| 2004 | 27 | 766,064 | 3.52 (2.42–5.14) | 2 | 5,616 | 35.6 (8.91–142) |
| 2005 | 39 | 805,582 | 4.84 (3.54–6.63) | 1 | 5,605 | 17.8 (2.51–127) |
| 2006 | 59 | 831,792 | 7.09 (5.50–9.15) | 2 | 5,453 | 36.7 (9.17–147) |
| 2007 | 67 | 860,350 | 7.79 (6.13–9.89) | 8 | 5,435 | 147 (73.6–294) |
| 2008 | 143 | 875,935 | 16.3 (13.9–19.2) | 10 | 5,208 | 192 (103–357) |
| 2009 | 312 | 883,603 | 35.3 (31.6–39.5) | 16 | 4,922 | 325 (199–531) |
| 2010 | 496 | 865,219 | 57.3 (52.5–62.6) | 19 | 4,512 | 421 (269–660) |
| 2011 | 901 | 872,353 | 103 (96.8–110) | 47 | 4,170 | 1,127 (847–1,500) |
| 2012 | 1,652 | 877,054 | 188 (179–198) | 70 | 3,825 | 1,830 (1,448–2,313) |
| 2013 | 1,839 | 841,381 | 219 (209–229) | 59 | 3,342 | 1,766 (1,368–2,279) |
| 2014 | 1,704 | 761,971 | 224 (213–235) | 44 | 2,656 | 1,657 (1,233–2,226) |

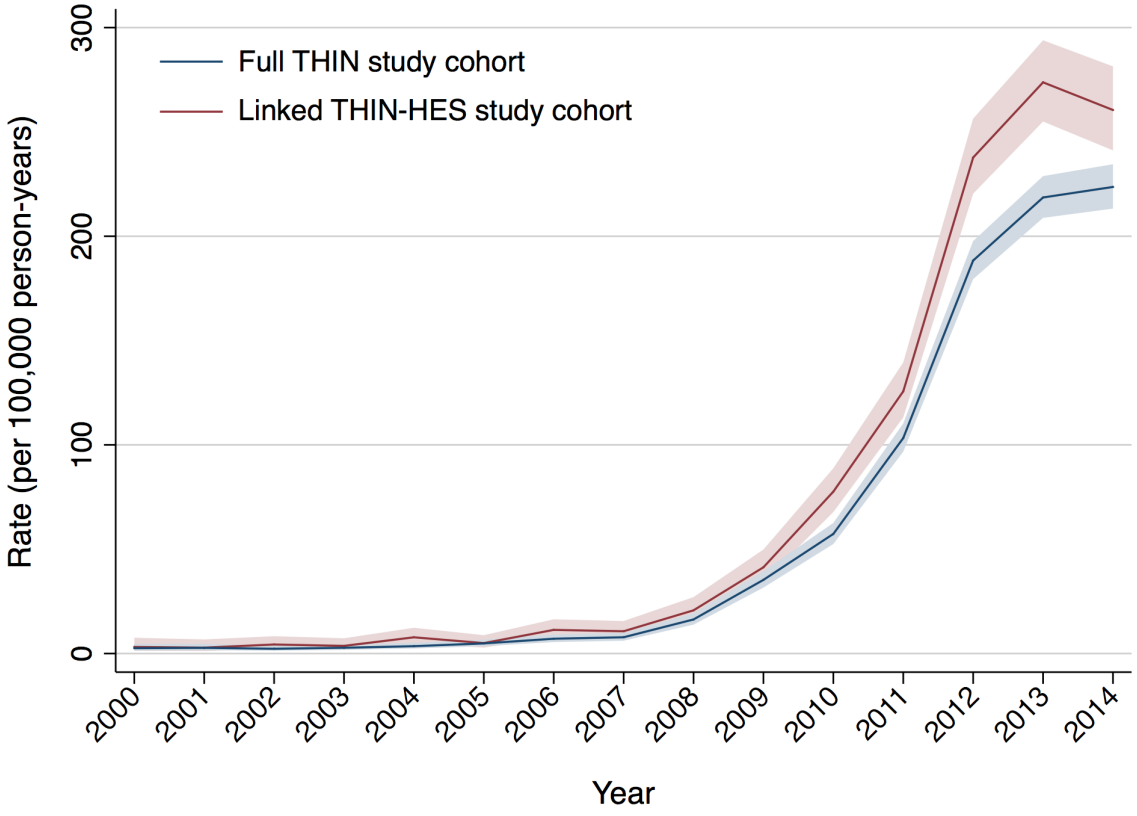
Abbreviations: CI, confidence interval; PYAR, person-years at risk.

[a] The analysis used the full study cohort, including children with a record of a medical condition that can predispose to vitamin D deficiency by interfering with vitamin D absorption or metabolism (chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption).

### 5.4.3.9 Time Trends in Diagnosis Using the Linked THIN-HES Study Cohort

Time trends in the diagnosis of vitamin D deficiency observed in the linked THIN-HES study cohort were similar to those seen in the full THIN study cohort, although overall rates of diagnosis were somewhat higher in the linked THIN-HES cohort compared to the full THIN cohort (Figure 5.14 and Table 5.22).

**Figure 5.14** Time trends in the diagnosis of vitamin D deficiency in the full THIN study cohort and in the linked THIN-HES study cohort, between 2000 and 2014.[a]




[a] Crude incidence rates are shown, with 95% confidence intervals represented by the shaded areas.

**Table 5.22** Crude incidence rates for the diagnosis of vitamin D deficiency in the full THIN study cohort and in the linked THIN-HES study cohort, by year between 2000 and 2014.

| Year | Full THIN study cohort (n= 2,338,529) | | | Linked THIN-HES study cohort (n=711,788) | | |
|---|---|---|---|---|---|---|
| | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) | No. of cases | PYAR | Incidence rate per 100,000 PYAR (95% CI) |
| 2000 | 11 | 430,721 | 2.55 (1.41–4.61) | 5 | 159,318 | 3.14 (1.31–7.54) |
| 2001 | 14 | 515,596 | 2.72 (1.61–4.58) | 5 | 177,945 | 2.81 (1.17–6.75) |
| 2002 | 14 | 614,946 | 2.28 (1.35–3.84) | 9 | 208,386 | 4.32 (2.25–8.30) |
| 2003 | 19 | 688,371 | 2.76 (1.76–4.33) | 8 | 219,036 | 3.65 (1.83–7.30) |
| 2004 | 27 | 766,064 | 3.52 (2.42–5.14) | 18 | 231,690 | 7.77 (4.89–12.3) |
| 2005 | 39 | 805,582 | 4.84 (3.54–6.63) | 12 | 240,543 | 4.99 (2.83–8.78) |
| 2006 | 59 | 831,792 | 7.09 (5.50–9.15) | 28 | 247,374 | 11.3 (7.82–16.4) |
| 2007 | 67 | 860,350 | 7.79 (6.13–9.89) | 27 | 253,053 | 10.7 (7.32–15.6) |
| 2008 | 143 | 875,935 | 16.3 (13.9–19.2) | 54 | 260,812 | 20.7 (15.9–27.0) |
| 2009 | 312 | 883,603 | 35.3 (31.6–39.5) | 110 | 266,102 | 41.3 (34.3–49.8) |
| 2010 | 496 | 865,219 | 57.3 (52.5–62.6) | 212 | 273,216 | 77.6 (67.8–88.8) |
| 2011 | 901 | 872,353 | 103 (96.8–110) | 351 | 279,387 | 126 (113–139) |
| 2012 | 1,652 | 877,054 | 188 (179–198) | 673 | 283,111 | 238 (220–256) |
| 2013 | 1,839 | 841,381 | 219 (209–229) | 761 | 277,985 | 274 (255–294) |
| 2014 | 1,704 | 761,971 | 224 (213–235) | 645 | 247,604 | 261 (241–281) |

Abbreviations: CI, confidence interval; PYAR, person-years at risk.

### 5.4.4 Differences in Rates of Diagnosis of Vitamin D Deficiency by Socio-Demographic Factors: Crude Associations

#### 5.4.4.1 Analysis Using the Full Study Cohort

In unadjusted analyses, vitamin D deficiency was diagnosed more frequently in girls compared to boys, in older children compared to younger children, and in children from more deprived backgrounds (Table 5.23). Children from minority ethnic groups were considerably more likely to be diagnosed with vitamin D deficiency than children from white ethnic backgrounds, although it should be noted that there was a large proportion of missing data for ethnicity (51.9%). Vitamin D deficiency was diagnosed more commonly in children residing in England compared to the other countries in the UK, and within England diagnosis rates were highest in children in London and the West Midlands. Rates of diagnosis increased markedly over time during the study period.

In separate analysis including children with medical conditions that can predispose to deficiency by interfering with vitamin D absorption or metabolism, vitamin D deficiency was diagnosed more frequently in children with liver disease (RR 8.78, 95% CI: 6.26 to 11.7, $p<0.001$), children with chronic renal disease (RR 4.82, 95% CI: 3.80 to 6.11, $p<0.001$), and children with conditions associated with gastrointestinal malabsorption (RR 6.41, 95% CI: 5.47 to 7.51, $p<0.001$) compared to children without any of these co-morbidities.

#### 5.4.4.2 Analysis Using the Linked THIN-HES Study Cohort

Crude associations between the study covariates and rates of diagnosis of vitamin D deficiency in the linked THIN-HES cohort were similar to the results of analyses using the full study cohort (Table 5.24).

**Table 5.23** Crude associations between each study covariate and the rate of diagnosis of vitamin D deficiency, in the full study cohort (n=2,338,529).

| Covariate | PYAR (100,000s) | No. of cases | Rate ratio (95% CI) | p-value [a] |
|---|---|---|---|---|
| ***Sex*** [b] | | | | |
| Male | 59.6 | 2,896 | Baseline | - |
| Female | 55.3 | 4,401 | 1.64 (1.54–1.72) | <0.001 |
| ***Age group*** [b] | | | | |
| 0 – 4 years | 31.1 | 1,152 | Baseline | - |
| 5 – 9 years | 32.9 | 1,377 | 1.13 (1.04–1.22) | 0.002 |
| 10 – 14 years | 32.3 | 2,652 | 2.22 (2.07–2.37) | <0.001 |
| 15 – 17 years | 18.7 | 2,116 | 3.05 (2.84–3.28) | <0.001 |
| ***Ethnicity*** [c] | | | | |
| White | 44.8 | 1,348 | Baseline | - |
| Asian or Asian British | 3.17 | 2,401 | 25.2 (23.6–26.9) | <0.001 |
| Black or black British | 1.86 | 1,091 | 19.5 (18.0–21.1) | <0.001 |
| Mixed | 1.10 | 227 | 6.83 (5.93–7.86) | <0.001 |
| Chinese or other ethnic group | 0.95 | 346 | 12.1 (10.7–13.6) | <0.001 |
| ***Townsend deprivation index quintile*** [d] | | | | |
| 1 (least deprived) | 28.1 | 681 | Baseline | - |
| 2 | 22.6 | 664 | 1.21 (1.09–1.35) | <0.001 |
| 3 | 22.8 | 1,295 | 2.34 (2.13–2.57) | <0.001 |
| 4 | 21.1 | 1,761 | 3.44 (3.15–3.76) | <0.001 |
| 5 (most deprived) | 15.4 | 1,964 | 5.26 (4.82–5.74) | <0.001 |
| ***Country*** [b] | | | | |
| England | 89.3 | 6,794 | Baseline | - |
| Scotland | 12.8 | 219 | 0.23 (0.20–0.26) | <0.001 |
| Wales | 8.32 | 234 | 0.37 (0.32–0.42) | <0.001 |
| Northern Ireland | 4.42 | 50 | 0.15 (0.11–0.20) | <0.001 |
| ***Strategic Health Authority*** [e] | | | | |
| South Central | 13.6 | 343 | Baseline | - |
| North West | 10.9 | 541 | 1.98 (1.73–2.27) | <0.001 |
| London | 10.7 | 2,924 | 10.8 (9.67–12.1) | <0.001 |
| South West | 10.3 | 100 | 0.39 (0.31–0.48) | <0.001 |
| South East Coast | 10.3 | 273 | 1.06 (0.90–1.24) | 0.485 |
| West Midlands | 9.88 | 1,592 | 6.40 (5.70–7.20) | <0.001 |
| East of England | 7.27 | 207 | 1.13 (0.95–1.35) | 0.158 |
| East Midlands | 3.75 | 111 | 1.18 (0.95–1.46) | 0.133 |
| Yorkshire & Humber | 3.34 | 46 | 0.55 (0.40–0.74) | <0.001 |
| North East | 2.69 | 113 | 1.67 (1.35–2.07) | <0.001 |

**Table 5.23** continued.

| Covariate | PYAR (100,000s) | No. of cases | Rate ratio (95% CI) | p-value |
|---|---|---|---|---|
| ***Calendar year*** [b] | | | | |
| 2000 | 4.31 | 11 | Baseline | - |
| 2001 | 5.16 | 14 | 1.06 (0.48–2.34) | 0.879 |
| 2002 | 6.15 | 14 | 0.89 (0.41–1.96) | 0.775 |
| 2003 | 6.88 | 19 | 1.08 (0.51–2.27) | 0.838 |
| 2004 | 7.66 | 27 | 1.38 (0.69–2.78) | 0.366 |
| 2005 | 8.06 | 39 | 1.90 (0.97–3.70) | 0.057 |
| 2006 | 8.32 | 59 | 2.78 (1.46–5.29) | 0.001 |
| 2007 | 8.60 | 67 | 3.05 (1.61–5.77) | <0.001 |
| 2008 | 8.76 | 143 | 6.39 (3.46–11.8) | <0.001 |
| 2009 | 8.84 | 312 | 13.8 (7.58–25.2) | <0.001 |
| 2010 | 8.65 | 496 | 22.4 (12.4–40.8) | <0.001 |
| 2011 | 8.72 | 901 | 40.4 (22.3–73.3) | <0.001 |
| 2012 | 8.77 | 1,652 | 73.8 (40.8–133) | <0.001 |
| 2013 | 8.41 | 1,839 | 85.6 (47.3–155) | <0.001 |
| 2014 | 7.62 | 1,704 | 87.6 (48.4–158) | <0.001 |

Abbreviations: CI, confidence interval; PYAR, person-years at risk.
[a] P-value for the null hypothesis that the true rate ratio is equal to 1.
[b] Complete data is available for these variables.
[c] Data missing for 51.9% of the cohort.
[d] Data missing for 6.2% of the cohort.
[e] Data missing for 6.0% of the cohort.

**Table 5.24** Crude associations between each study covariate and the rate of diagnosis of vitamin D deficiency, in the linked THIN-HES study cohort (n=711,788).

| Covariate | PYAR (100,000s) | No. of cases | Rate ratio (95% CI) | p-value [a] |
|---|---|---|---|---|
| ***Sex*** [b] | | | | |
| Male | 18.8 | 1,133 | Baseline | - |
| Female | 17.4 | 1,785 | 1.70 (1.58–1.83) | <0.001 |
| ***Age group*** [b] | | | | |
| 0 – 4 years | 9.97 | 400 | Baseline | - |
| 5 – 9 years | 10.4 | 558 | 1.33 (1.17–1.51) | <0.001 |
| 10 – 14 years | 10.1 | 1,161 | 2.86 (2.56–3.21) | <0.001 |
| 15 – 17 years | 5.74 | 799 | 3.47 (3.08–3.91) | <0.001 |
| ***Ethnicity*** [c] | | | | |
| White | 26.8 | 635 | Baseline | - |
| Asian or Asian British | 0.63 | 1,203 | 33.1 (30.0–36.4) | <0.001 |
| Black or black British | 1.53 | 585 | 25.3 (22.6–28.3) | <0.001 |
| Mixed | 0.98 | 117 | 7.83 (6.43–9.54) | <0.001 |
| Chinese or other ethnic group | 0.53 | 156 | 12.5 (10.5–14.8) | <0.001 |
| ***Townsend deprivation index quintile*** [d] | | | | |
| 1 (least deprived) | 9.98 | 171 | Baseline | - |
| 2 | 7.00 | 205 | 1.71 (1.39–2.09) | <0.001 |
| 3 | 7.50 | 561 | 4.36 (3.68–5.18) | <0.001 |
| 4 | 6.68 | 741 | 6.48 (5.48–7.65) | <0.001 |
| 5 (most deprived) | 4.04 | 697 | 10.1 (8.51–11.9) | <0.001 |
| ***Index of Multiple Deprivation quintile*** [e] | | | | |
| 1 (least deprived) | 9.25 | 172 | Baseline | - |
| 2 | 7.31 | 333 | 2.45 (2.04–2.94) | <0.001 |
| 3 | 7.16 | 520 | 3.90 (3.29–4.64) | <0.001 |
| 4 | 6.88 | 635 | 4.97 (4.20–5.88) | <0.001 |
| 5 (most deprived) | 4.68 | 648 | 7.44 (6.29–8.80) | <0.001 |
| ***Strategic Health Authority*** [b] | | | | |
| South Central | 8.25 | 165 | Baseline | - |
| North West | 3.54 | 100 | 1.41 (1.10–1.81) | 0.006 |
| London | 4.28 | 1,295 | 15.1 (12.9–17.8) | <0.001 |
| South West | 5.79 | 51 | 0.44 (0.32–0.60) | <0.001 |
| South East Coast | 4.67 | 123 | 1.32 (1.04–1.66) | 0.020 |
| West Midlands | 4.63 | 971 | 10.5 (8.90–12.4) | <0.001 |
| East of England | 3.06 | 102 | 1.67 (1.30–2.13) | <0.001 |
| East Midlands | 0.24 | 0 | - | - |
| Yorkshire & Humber | 0.80 | 12 | 0.75 (0.42–1.35) | 0.334 |
| North East | 1.00 | 99 | 4.97 (3.88–6.38) | <0.001 |

**Table 5.24** continued.

| Covariate | PYAR (100,000s) | No. of cases | Rate ratio (95% CI) | p-value |
|---|---|---|---|---|
| ***Calendar year*** [b] | | | | |
| 2000 | 1.59 | 5 | Baseline | - |
| 2001 | 1.78 | 5 | 0.90 (0.26–3.09) | 0.861 |
| 2002 | 2.08 | 9 | 1.38 (0.46–4.11) | 0.565 |
| 2003 | 2.19 | 8 | 1.16 (0.38–3.56) | 0.790 |
| 2004 | 2.32 | 18 | 2.48 (0.92–6.67) | 0.064 |
| 2005 | 2.41 | 12 | 1.59 (0.56–4.51) | 0.380 |
| 2006 | 2.47 | 28 | 3.61 (1.39–9.34) | 0.005 |
| 2007 | 2.53 | 27 | 3.40 (1.31–8.83) | 0.008 |
| 2008 | 2.61 | 54 | 6.60 (2.64–16.5) | <0.001 |
| 2009 | 2.66 | 110 | 13.2 (5.38–32.3) | <0.001 |
| 2010 | 2.73 | 212 | 24.7 (10.2–60.0) | <0.001 |
| 2011 | 2.79 | 351 | 40.0 (16.6–96.8) | <0.001 |
| 2012 | 2.83 | 673 | 75.7 (31.4–183) | <0.001 |
| 2013 | 2.78 | 761 | 87.2 (36.2–210) | <0.001 |
| 2014 | 2.48 | 645 | 83.0 (34.4–200) | <0.001 |

Abbreviations: CI, confidence interval; PYAR, person-years at risk.
[a] P-value for the null hypothesis that the true rate ratio is equal to 1.
[b] Complete data is available for these variables.
[c] Data missing for 18.5% of the cohort.
[d] Data missing for 4.3% of the cohort.
[e] Data missing for 6.7% of the cohort.

### *5.4.5 Differences in Rates of Diagnosis of Vitamin D Deficiency by Socio-Demographic Factors: Multivariable Analyses*

#### *5.4.5.1 Single Level Poisson Regression Models, Without Interactions Between Covariates*

In multivariable analysis, female sex, older age, non-white ethnicity, and greater socio-economic deprivation (measured using the Index of Multiple Deprivation) remained strongly associated with higher rates of vitamin D deficiency diagnosis (Table 5.25). After accounting for temporal changes in socio-demographic factors, a 15-fold increase in diagnosis (95% CI: 10 to 21) was seen between 2008 to 2014. The magnitude of the effects of IMD and ethnicity were somewhat reduced after adjustment for the other study covariates. The magnitude of the effects of the other study covariates were similar in the crude and adjusted analyses.

**Table 5.25** Adjusted associations between the study covariates and the rate of diagnosis of vitamin D deficiency, using single-level Poisson regression with socio-economic position measured using the IMD (n=414,182).

| Covariate | Unadjusted RR (95% CI) [a] | Adjusted RR (95% CI) [b] | LRT p-value [c] |
|---|---|---|---|
| ***Sex*** | | | <0.001 |
| Male | Baseline | Baseline | |
| Female | 1.69 (1.57–1.83) | 1.63 (1.49–1.78) | |
| ***Age group*** | | | <0.001 |
| 0 – 4 years | Baseline | Baseline | |
| 5 – 9 years | 1.51 (1.32–1.73) | 1.45 (1.25–1.69) | |
| 10 – 14 years | 3.18 (2.82–3.58) | 3.79 (3.31–4.34) | |
| 15 – 17 years | 3.71 (3.27–4.20) | 4.91 (4.25–5.67) | |
| ***Ethnicity*** [d] | | | <0.001 |
| White | Baseline | Baseline | |
| Asian or Asian British | 25.5 (24.0–29.2) | 22.4 (20.1–24.9) | |
| Black or black British | 20.6 (18.4–23.1) | 14.2 (12.5–16.2) | |
| Mixed | 6.07 (4.97–7.41) | 5.64 (4.52–7.03) | |
| Chinese or other ethnic group | 10.5 (8.79–12.5) | 8.91 (7.38–10.8) | |
| ***IMD quintile*** | | | <0.001 |
| 1 (least deprived) | Baseline | Baseline | |
| 2 | 2.40 (1.99–2.89) | 1.98 (1.63–2.41) | |
| 3 | 3.89 (3.27–4.63) | 2.40 (2.00–2.88) | |
| 4 | 4.82 (4.07–5.72) | 2.67 (2.23–3.20) | |
| 5 (most deprived) | 7.38 (6.23–8.75) | 3.54 (2.96–4.24) | |
| ***Calendar year*** | | | |
| 2008 | Baseline | Baseline | <0.001 |
| 2009 | 2.00 (1.44–2.77) | 2.20 (1.45–3.35) | |
| 2010 | 3.75 (2.78–5.05) | 3.87 (2.62–5.71) | |
| 2011 | 6.07 (4.56–8.08) | 6.61 (4.55–9.60) | |
| 2012 | 11.5 (8.70–15.1) | 12.7 (8.83–18.2) | |
| 2013 | 13.2 (10.0–17.4) | 14.7 (10.2–21.1) | |
| 2014 | 12.6 (9.53–16.6) | 14.7 (10.2–21.2) | |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; LRT, likelihood ratio test; RR, rate ratio.

[a] Crude associations between incidence rates and each study covariate separately.

[b] Results from a single-level multivariable Poisson regression model, adjusted for all variables listed in the table. Missing data was handled using complete cases analysis. n=414,182.

[c] P values from LRTs comparing nested models with and without the variable of interest.

[d] Ethnicity data was available from the child's THIN or HES record for 84.6% of included children. Maternal ethnicity was used as a proxy measure for the remaining 15.4%.

Similar results were obtained when socio-economic position was measured using the Townsend Index as opposed to the IMD (Table 5.26). The IMD was used in subsequent analyses, on the basis that it is derived from a considerably broader range of indicator variables than the Townsend Index (see section 5.3.5.3).

**Table 5.26** Adjusted associations between the study covariates and the rate of diagnosis of vitamin D deficiency, using single-level Poisson regression with socio-economic position measured using the Townsend Index (n=423,817).

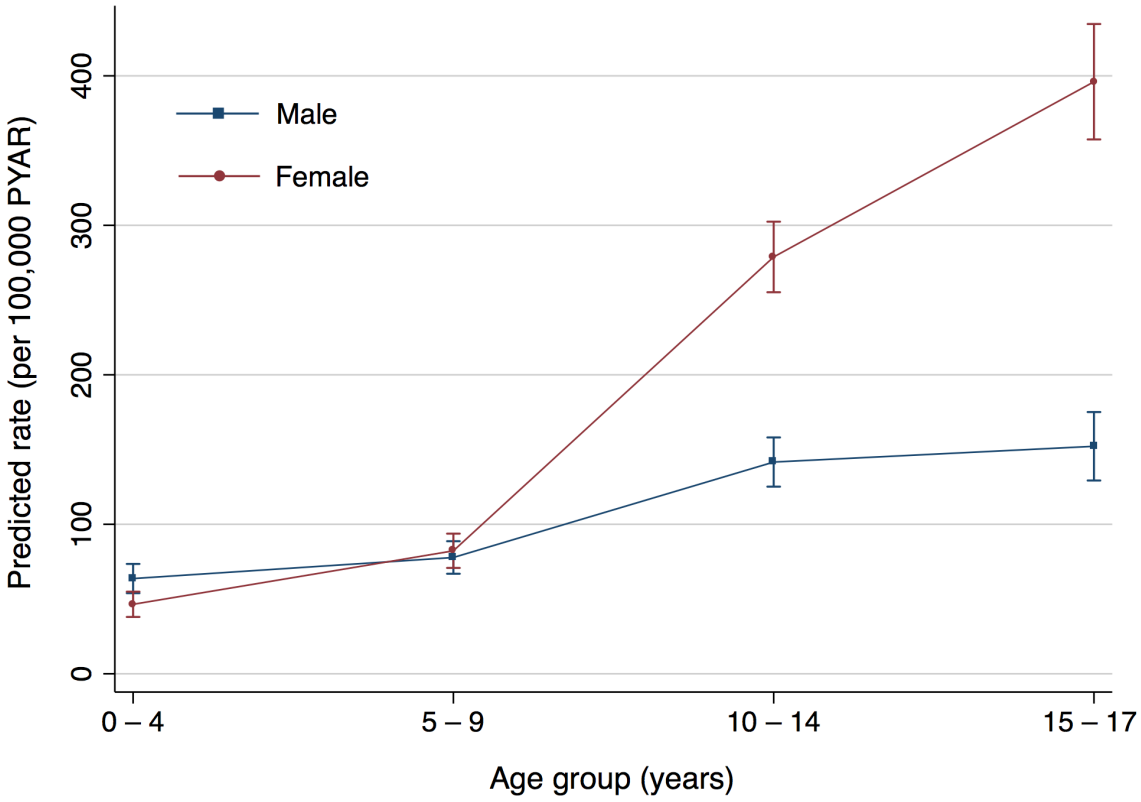
| Covariate | Unadjusted RR (95% CI) [a] | Adjusted RR (95% CI) [b] | LRT p-value [c] |
|---|---|---|---|
| ***Sex*** | | | <0.001 |
| Male | Baseline | Baseline | |
| Female | 1.69 (1.57–1.83) | 1.62 (1.48–1.77) | |
| ***Age group*** | | | <0.001 |
| 0 – 4 years | Baseline | Baseline | |
| 5 – 9 years | 1.51 (1.32–1.73) | 1.50 (1.29–1.75) | |
| 10 – 14 years | 3.18 (2.82–3.58) | 3.88 (3.39–4.44) | |
| 15 – 17 years | 3.71 (3.27–4.20) | 4.98 (4.32–5.74) | |
| ***Ethnicity*** [d] | | | <0.001 |
| White | Baseline | Baseline | |
| Asian or Asian British | 25.5 (24.0–29.2) | 20.5 (18.4–22.8) | |
| Black or black British | 20.6 (18.4–23.1) | 12.5 (11.0–14.3) | |
| Mixed | 6.07 (4.97–7.41) | 5.14 (4.12–6.42) | |
| Chinese or other ethnic group | 10.5 (8.79–12.5) | 8.24 (6.83–9.93) | |
| ***Townsend Index quintile*** | | | <0.001 |
| 1 (least deprived) | Baseline | Baseline | |
| 2 | 1.68 (1.37–2.06) | 1.48 (1.19–1.84) | |
| 3 | 4.24 (3.56–5.05) | 2.66 (2.21–3.19) | |
| 4 | 6.11 (5.16–7.24) | 3.12 (2.61–3.73) | |
| 5 (most deprived) | 9.62 (8.12–11.4) | 4.11 (3.43–4.93) | |
| ***Calendar year*** | | | |
| 2008 | Baseline | Baseline | <0.001 |
| 2009 | 2.00 (1.44–2.77) | 2.17 (1.46–3.22) | |
| 2010 | 3.75 (2.78–5.05) | 3.36 (2.32–4.87) | |
| 2011 | 6.07 (4.56–8.08) | 5.85 (4.11–8.33) | |
| 2012 | 11.5 (8.70–15.1) | 11.3 (8.01–15.9) | |
| 2013 | 13.2 (10.0–17.4) | 13.1 (9.30–18.4) | |
| 2014 | 12.6 (9.53–16.6) | 13.4 (9.49–18.8) | |

Abbreviations: CI, confidence interval; LRT, likelihood ratio test; RR, rate ratio.
[a] Crude associations between incidence rates and each study covariate separately.
[b] Results from a single-level multivariable Poisson regression model, adjusted for all variables listed in the table. Missing data was handled using complete cases analysis. n=423,817.
[c] P values from LRTs comparing nested models with and without the variable of interest.
[d] Ethnicity data was available from the child's THIN or HES record for 83.8% of included children. Maternal ethnicity was used as a proxy measure for the remaining 16.2%.

### 5.4.5.2 Examination of Interactions Between Model Covariates

A significant interaction between sex and age group was seen (LRT p-value <0.001); among children aged ≥10 years girls exhibited higher rates of vitamin D deficiency diagnosis than boys, whilst among children aged <5 years boys exhibited higher rates than girls (Figure 5.15 and Table 5.27). There was no difference in rates of diagnosis between boys and girls aged between 5 to 9 years.

**Figure 5.15** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of age, showing an interaction with sex.[a]




Abbreviations: PYAR, person-years at risk.
[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (ethnicity, Index of Multiple Deprivation, and calendar year). The vertical bars represent 95% confidence intervals. Missing data was handled using complete cases analysis. n=414,182.

There was no evidence of any important interactions between the other study covariates, as inclusion of interaction terms did not result in qualitative changes in parameter rate ratios (see appendix E). The interaction between sex and age group was retained in the multivariable regression model (Table 5.27).

**Table 5.27** Adjusted associations between the study covariates and the rate of diagnosis of vitamin D deficiency, using single-level Poisson regression with an interaction between sex and age group (n=414,182).

| Covariate | | Adjusted RR (95% CI) [a] | p-value [b] |
|---|---|---|---|
| ***Sex***, *stratified by age group* | | | <0.001 |
| *0 – 4 years:* | Male | Baseline | |
| | Female | 0.73 (0.57–0.93) | |
| *5 – 9 years:* | Male | Baseline | |
| | Female | 1.06 (0.87–1.29) | |
| *10 – 14 years:* | Male | Baseline | |
| | Female | 1.97 (1.71–2.27) | |
| *15 – 17 years:* | Male | Baseline | |
| | Female | 2.60 (2.18–3.11) | |
| ***Age group***, *stratified by sex* | | | <0.001 |
| *Males:* | 0 – 4 years | Baseline | |
| | 5 – 9 years | 1.22 (0.99–1.50) | |
| | 10 – 14 years | 2.22 (1.83–2.70) | |
| | 15 – 17 years | 2.39 (1.93–2.96) | |
| *Females:* | 0 – 4 years | Baseline | |
| | 5 – 9 years | 1.77 (1.41–2.23) | |
| | 10 – 14 years | 6.00 (4.91–7.34) | |
| | 15 – 17 years | 8.52 (6.93–10.5) | |
| ***Ethnicity*** | | | <0.001 |
| White | | Baseline | |
| Asian or Asian British | | 22.4 (20.1–24.9) | |
| Black or black British | | 14.2 (12.5–16.2) | |
| Mixed | | 5.64 (4.52–7.03) | |
| Chinese or other ethnic group | | 8.91 (7.38–10.8) | |
| ***IMD quintile*** | | | <0.001 |
| 1 (least deprived) | | Baseline | |
| 2 | | 1.98 (1.63–2.41) | |
| 3 | | 2.40 (2.00–2.88) | |
| 4 | | 2.67 (2.23–3.20) | |
| 5 (most deprived) | | 3.54 (2.96–4.24) | |
| ***Calendar year*** | | | <0.001 |
| 2008 | | Baseline | |
| 2009 | | 2.20 (1.45–3.35) | |
| 2010 | | 3.87 (2.62–5.71) | |
| 2011 | | 6.61 (4.55–9.60) | |
| 2012 | | 12.7 (8.83–18.2) | |
| 2013 | | 14.7 (10.2–21.1) | |
| 2014 | | 14.7 (10.2–21.2) | |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results from a single-level multivariable Poisson regression model, adjusted for all variables listed in the table, including an interaction between sex and age group. Likelihood ratio test (LRT) for interaction p-value <0.001. Missing data was handled using complete cases analysis.
[b] p-values from LRTs comparing nested models with & without variables of interest.

#### 5.4.5.3 Multilevel Models Accounting for the Clustered Structure of the Data

Table 5.28 shows the results of multivariable analyses using both the single-level Poisson regression model, as well as a two-level mixed-effects model that accounts for the clustering of children within general practices. The magnitude of the effects of ethnicity and socio-economic deprivation were attenuated after accounting for clustering by practice, however they both remained strongly associated with rates of diagnosis of vitamin D deficiency. Associations between the other covariates (sex, age group, and calendar year) and the outcome were very similar in the single-level and multilevel analyses.

Results obtained from a three-level mixed-effects Poisson regression model, which additionally accounted for the nesting of practices within strategic health authority regions, were essentially the same as those obtained from the two-level model (Table 5.29).

**Table 5.28** Adjusted associations between study covariates and diagnosis of vitamin D deficiency, with and without accounting for clustering by practice (n=414,182).[a]

| Covariate | | Single-level Model | | Multilevel Model | |
|---|---|---|---|---|---|
| | | Adjusted RR (95% CI) | p-value [b] | Adjusted RR (95% CI) | p-value [b] |
| ***Sex***, *stratified by age group* | | | <0.001 | | <0.001 |
| *0 – 4 years:* | Male | Baseline | | Baseline | |
| | Female | 0.73 (0.57–0.93) | | 0.72 (0.57–0.92) | |
| *5 – 9 years:* | Male | Baseline | | Baseline | |
| | Female | 1.06 (0.87–1.29) | | 1.04 (0.86–1.27) | |
| *10 – 14 years:* | Male | Baseline | | Baseline | |
| | Female | 1.97 (1.71–2.27) | | 1.97 (1.71– 2.27) | |
| *15 – 17 years:* | Male | Baseline | | Baseline | |
| | Female | 2.60 (2.18–3.11) | | 2.65 (2.21–3.16) | |
| ***Age group***, *stratified by sex* | | | <0.001 | | <0.001 |
| *Males* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.22 (0.99–1.50) | | 1.20 (0.98–1.48) | |
| | 10 – 14 years | 2.22 (1.83–2.70) | | 2.19 (1.80–2.65) | |
| | 15 – 17 years | 2.39 (1.93–2.96) | | 2.36 (1.90–2.93) | |
| *Females:* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.77 (1.41–2.23) | | 1.73 (1.37–2.18) | |
| | 10 – 14 years | 6.00 (4.91–7.34) | | 5.95 (4.86–7.27) | |
| | 15 – 17 years | 8.52 (6.93–10.5) | | 8.61 (7.00–10.6) | |
| ***Ethnicity*** | | | <0.001 | | <0.001 |
| White | | Baseline | | Baseline | |
| Asian or Asian British | | 22.4 (20.1–24.9) | | 7.98 (6.98–9.13) | |
| Black or black British | | 14.2 (12.5–16.2) | | 5.47 (4.70–6.37) | |
| Mixed | | 5.64 (4.52–7.03) | | 2.99 (2.38–3.76) | |
| Chinese or other ethnic group | | 8.91 (7.38–10.8) | | 3.63 (2.96–4.45) | |
| ***IMD quintile*** | | | <0.001 | | <0.001 |
| 1 (least deprived) | | Baseline | | Baseline | |
| 2 | | 1.98 (1.63–2.41) | | 1.34 (1.07–1.67) | |
| 3 | | 2.40 (2.00–2.88) | | 1.41 (1.12–1.77) | |
| 4 | | 2.67 (2.23–3.20) | | 1.63 (1.29–2.05) | |
| 5 (most deprived) | | 3.54 (2.96–4.24) | | 1.96 (1.52–2.53) | |
| ***Calendar year*** | | | <0.001 | | <0.001 |
| 2008 | | Baseline | | Baseline | |
| 2009 | | 2.20 (1.45–3.35) | | 2.19 (1.44–3.34) | |
| 2010 | | 3.87 (2.62–5.71) | | 3.66 (2.48–5.40) | |
| 2011 | | 6.61 (4.55–9.60) | | 6.28 (4.32–9.12) | |
| 2012 | | 12.7 (8.83–18.2) | | 12.1 (8.43–17.4) | |
| 2013 | | 14.7 (10.2–21.1) | | 14.1 (9.85–20.3) | |
| 2014 | | 14.7 (10.2–21.2) | | 15.7 (10.9–22.6) | |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency, adjusted for all listed variables and including an interaction term between age group and sex. Missing data is handled using complete cases analysis. The multilevel model additionally includes the general practice as a random effect.
[b] p-values from likelihood ratio tests comparing nested models with & without each variable.

**Table 5.29** Associations between study covariates and diagnosis of vitamin D deficiency, with and without accounting for nesting of practices within SHA regions.[a]

| Covariate | | Two-level Model | | Three-level Model | |
|---|---|---|---|---|---|
| | | Adjusted RR (95% CI) | p-value [b] | Adjusted RR (95% CI) | p-value [b] |
| ***Sex***, *stratified by age group* | | | <0.001 | | <0.001 |
| *0 – 4 years:* | Male | Baseline | | Baseline | |
| | Female | 0.72 (0.57–0.92) | | 0.72 (0.57–0.92) | |
| *5 – 9 years:* | Male | Baseline | | Baseline | |
| | Female | 1.04 (0.86–1.27) | | 1.04 (0.86–1.27) | |
| *10 – 14 years:* | Male | Baseline | | Baseline | |
| | Female | 1.97 (1.71– 2.27) | | 1.97 (1.71– 2.27) | |
| *15 – 17 years:* | Male | Baseline | | Baseline | |
| | Female | 2.65 (2.21–3.16) | | 2.65 (2.21–3.16) | |
| ***Age group***, *stratified by sex* | | | <0.001 | | <0.001 |
| *Males* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.20 (0.98–1.48) | | 1.20 (0.98–1.48) | |
| | 10 – 14 years | 2.19 (1.80–2.65) | | 2.19 (1.81–2.66) | |
| | 15 – 17 years | 2.36 (1.90–2.93) | | 2.36 (1.90–2.93) | |
| *Females:* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.73 (1.37–2.18) | | 1.73 (1.37–2.17) | |
| | 10 – 14 years | 5.95 (4.86–7.27) | | 5.95 (4.86–7.27) | |
| | 15 – 17 years | 8.61 (7.00–10.6) | | 8.62 (7.01–10.6) | |
| ***Ethnicity*** | | | <0.001 | | <0.001 |
| White | | Baseline | | Baseline | |
| Asian or Asian British | | 7.98 (6.98–9.13) | | 7.64 (6.69–8.73) | |
| Black or black British | | 5.47 (4.70–6.37) | | 5.20 (4.47–6.05) | |
| Mixed | | 2.99 (2.38–3.76) | | 2.87 (2.28–3.61) | |
| Chinese or other ethnic group | | 3.63 (2.96–4.45) | | 3.45 (2.82–4.23) | |
| ***IMD quintile*** | | | <0.001 | | <0.001 |
| 1 (least deprived) | | Baseline | | Baseline | |
| 2 | | 1.34 (1.07–1.67) | | 1.27 (1.02–1.58) | |
| 3 | | 1.41 (1.12–1.77) | | 1.32 (1.06–1.65) | |
| 4 | | 1.63 (1.29–2.05) | | 1.53 (1.22–1.92) | |
| 5 (most deprived) | | 1.96 (1.52–2.53) | | 1.85 (1.44–2.38) | |
| ***Calendar year*** | | | <0.001 | | <0.001 |
| 2008 | | Baseline | | Baseline | |
| 2009 | | 2.19 (1.44–3.34) | | 2.19 (1.44–3.34) | |
| 2010 | | 3.66 (2.48–5.40) | | 3.66 (2.48–5.40) | |
| 2011 | | 6.28 (4.32–9.12) | | 6.29 (4.33–9.14) | |
| 2012 | | 12.1 (8.43–17.4) | | 12.1 (8.44–17.5) | |
| 2013 | | 14.1 (9.85–20.3) | | 14.1 (9.83–20.3) | |
| 2014 | | 15.7 (10.9–22.6) | | 15.8 (11.0–22.7) | |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; LRT, likelihood ratio test; RR, rate ratio; SHA, strategic health authority.

[a] Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency, adjusted for all listed variables and including an interaction term between age group and sex. Missing data is handled using complete cases analysis. Both models include the general practice as a random effect. The 3-level model additionally accounts for nesting of practices within SHAs. p-values are from LRTs comparing nested models with & without each variable. n=414,182.

#### 5.4.5.4 Sensitivity Analysis Using Multiply Imputed Data

Table 5.31 shows the results of the multivariable Poisson regression models when missing data was handled using multiple imputation. These are very similar to the results of the main analyses using complete cases (Table 5.28).

### 5.4.6 Investigation of Recorded Symptoms Among Children Diagnosed with Vitamin D Deficiency

Among the 7,297 children in the full THIN study cohort with a diagnosis of vitamin D deficiency, 3,061 (42%) had a relevant symptom code recorded in their primary care electronic health record in the 6 months either side of the initial diagnosis. 312 children (4.3%) had a symptom from more than one symptom group recorded. Among those with a relevant symptom code recorded, the proportion of children with a code from each symptom category is shown in Table 5.30. The most commonly recorded symptoms were those related to musculoskeletal or non-specific pain, and tiredness or fatigue.

**Table 5.30** Frequency of each symptom category, among children with a relevant symptom code recorded in proximity to the date of initial diagnosis of vitamin D deficiency (n=3,061).

| Symptom Category | n (%) [a] |
|---|---|
| Musculoskeletal and non-specific pain | 1,916 (62.6%) |
| Tiredness and fatigue | 919 (30.0%) |
| Skeletal deformity | 136 (4.44%) |
| Bone fracture | 115 (3.76%) |
| Failure to thrive | 112 (3.66%) |
| Hypocalcaemia | 43 (1.40%) |
| Seizure or tetany | 41 (1.34%) |
| Numbness or paraesthesia | 33 (1.08%) |
| Abnormal gait | 31 (1.01%) |
| Muscle weakness | 26 (0.85%) |
| Delay in motor development | 6 (0.20%) |
| Cardiomyopathy | 5 (0.16%) |

[a] The sum of the percentages is greater than 100, because 10% of the children had symptoms recorded from more than one category.

**Table 5.31** Associations between study covariates and diagnosis of vitamin D deficiency, with missing data handled using multiple imputation (n=511,868).[a]

| Covariate | | Single-level Model | | Multilevel Model | |
|---|---|---|---|---|---|
| | | Adjusted IRR [b] (95% CI) | p-value [c] | Adjusted IRR [b] (95% CI) | p-value [c] |
| ***Sex***, *stratified by age group* | | | <0.001 | | <0.001 |
| *0 – 4 years:* | Male | Baseline | | Baseline | |
| | Female | 0.78 (0.64–0.97) | | 0.78 (0.63–0.96) | |
| *5 – 9 years:* | Male | Baseline | | Baseline | |
| | Female | 1.18 (1.00–1.41) | | 1.18 (1.00–1.40) | |
| *10 – 14 years:* | Male | Baseline | | Baseline | |
| | Female | 1.98 (1.75–2.24) | | 1.99 (1.76–2.25) | |
| *15 – 17 years:* | Male | Baseline | | Baseline | |
| | Female | 2.57 (2.20–3.00) | | 2.63 (2.25–3.06) | |
| ***Age group***, *stratified by sex* | | | <0.001 | | <0.001 |
| *Males* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.28 (1.07–1.54) | | 1.26 (1.05–1.52) | |
| | 10 – 14 years | 2.30 (1.94–2.72) | | 2.26 (1.90–2.67) | |
| | 15 – 17 years | 2.39 (1.98–2.89) | | 2.37 (1.96–2.87) | |
| *Females:* | 0 – 4 years | Baseline | | Baseline | |
| | 5 – 9 years | 1.94 (1.60–2.26) | | 1.92 (1.58–2.33) | |
| | 10 – 14 years | 5.81 (4.89–6.91) | | 5.77 (4.85–6.86) | |
| | 15 – 17 years | 7.82 (6.54–9.36) | | 8.00 (6.68–9.56) | |
| ***Ethnicity*** [d] | | | <0.001 | | <0.001 |
| White | | Baseline | | Baseline | |
| Asian or Asian British | | 21.8 (19.8–24.0) | | 7.14 (6.31–8.07) | |
| Black or black British | | 15.3 (13.6–17.1) | | 5.42 (4.74–6.20) | |
| Mixed | | 5.85 (4.80–7.14) | | 2.97 (2.42–3.65) | |
| Chinese or other ethnic group | | 8.56 (7.18–10.2) | | 3.41 (2.82–4.13) | |
| ***IMD quintile*** [e] | | | <0.001 | | <0.001 |
| 1 (least deprived) | | 1 | | 1 | |
| 2 | | 2.01 (1.67–2.42) | | 1.33 (1.08–1.65) | |
| 3 | | 2.48 (2.08–2.95) | | 1.47 (1.18–1.83) | |
| 4 | | 2.94 (2.48–3.49) | | 1.70 (1.36–2.13) | |
| 5 (most deprived) | | 4.51 (3.82–5.32) | | 1.94 (1.52–2.48) | |
| ***Calendar year*** | | | <0.001 | | <0.001 |
| 2008 | | Baseline | | Baseline | |
| 2009 | | 1.95 (1.41–2.71) | | 1.95 (1.40–2.70) | |
| 2010 | | 3.54 (2.62–4.78) | | 3.34 (2.47–4.51) | |
| 2011 | | 5.63 (4.21–7.51) | | 5.34 (4.00–7.13) | |
| 2012 | | 10.4 (7.87–13.8) | | 9.95 (7.52–13.2) | |
| 2013 | | 11.8 (8.93–15.6) | | 11.4 (8.63–15.1) | |
| 2014 | | 12.2 (9.21–16.1) | | 12.9 (9.70–17.0) | |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency. Missing data is handled using multivariable multiple imputation.
[b] Adjusted for all variables listed in the table, including an interaction term between age and sex (likelihood ratio test for interaction p value<0.001). The multilevel model additionally includes the general practice as a random effect.
[c] p-values from likelihood ratio tests comparing nested models with & without each variable.
[d] Ethnicity data was available from the child's THIN or HES record for 73.4% of children, maternal ethnicity was used as a proxy measure for 13.9%, and it was imputed for the remaining 12.7%.
[e] IMD was available from the THIN record for 91.7% of children, and was imputed for 8.3%.

## 5.5 Discussion

### *5.5.1 Summary of Results and Comparison with Existing Studies*

#### *5.5.1.1 Time Trends in the Diagnosis of Vitamin D Deficiency*

A marked increase in the diagnosis of vitamin D deficiency in clinical practice was observed among children in the UK over the past decade. Prior to 2008, overall rates of diagnosis of vitamin D deficiency were below 10 per 100,000 person-years. Between 2008 and 2013 this increased to over 200 per 100,000 person-years, after which rates plateaued between 2013 to 2014. After accounting for temporal changes in socio-demographic factors within the cohort (age, sex, ethnicity, and Index of Multiple Deprivation), an increase in diagnosis of approximately 15-fold (95% CI: 10 to 21) was seen between 2008 to 2014.

This is the first study to report estimates for overall rates of diagnosis of vitamin D deficiency in clinical practice, either among children or adults, in the UK or internationally. Therefore, the observed rates of diagnosis cannot be directly compared with existing research. A number of previous studies have investigated the incidence of symptomatic vitamin D deficiency in children presenting to secondary care services (see chapter 3). In contrast to these reports, the current study includes all children diagnosed with or treated for vitamin D deficiency irrespective of the presence of clinical symptoms, and captures children in primary as well as secondary care. Studies from the UK, Denmark, Canada, and New Zealand have provided annual incidence estimates for symptomatic vitamin D deficiency in secondary care of between 2.2 to 7.5 per 100,000 children (Beck-Nielsen et al, 2009a; Callaghan et al, 2006; El-Fakhri et al, 2013; Ward et al, 2007; Wheeler et al, 2015). Whilst the rates of diagnosis of vitamin D deficiency observed in the earlier years of this study (prior to 2008) are comparable with these figures, it is clear that the rates of diagnosis observed in more recent years are considerably higher.

Although time trends in rates of diagnosis of vitamin D deficiency have not been previously reported, trends in vitamin D testing among the general population in Australia (including adults and children) have shown a similar large increase over time (Bilinski & Boyages, 2013). National rates of 25-OH-D testing in Australia increased over 50-fold from 59 tests per 100,000 people in 2001 to 3,648 tests per 100,000 people in 2011.

#### 5.5.1.2 Associations Between Socio-Demographic Factors and the Diagnosis of Vitamin D Deficiency

Vitamin D deficiency was diagnosed considerably more frequently in children from minority ethnic groups compared to children from white ethnic backgrounds. In the single-level model, diagnosis rates were 22-fold higher in Asian children (95% CI: 20 to 25), and 14-fold higher in black children (95% CI: 13 to 16), when compared to white children. It is not surprising that vitamin D deficiency was diagnosed more frequently in these groups, as pigmented skin is well known to be an important risk factor for vitamin D deficiency; children from non-white backgrounds have lower vitamin D levels than white children (Absoud et al, 2011; Gordon et al, 2004; Mansbach et al, 2009; Petersen et al, 2016b; Tolppanen et al, 2012), and children from South Asian and black backgrounds are at highest risk of symptomatic vitamin D deficiency (Ahmed et al, 2011; Callaghan et al, 2006; El-Fakhri et al, 2013; Ladhani et al, 2004; Sharma et al, 2009).

Vitamin D deficiency was also diagnosed more frequently in children from more deprived backgrounds, independent of ethnicity. This association was consistent when two different area-based measures of socio-economic position (SEP) were used (the Townsend Index and the Index of Multiple Deprivation). In the single-level model, the rate ratio for diagnosis in children from the most deprived compared to the least deprived IMD quintile was 3.5 (95% CI: 3.0 to 4.2). Lower socio-economic position, measured using a variety of indicators in different studies, has been associated with lower vitamin D levels in children independent of ethnicity (Absoud et al, 2011; Tolppanen et al, 2012; Turer et al, 2013), and with reduced use of vitamin D supplements among infants and school aged children (Millette et al, 2014; Munasinghe et al, 2015). Another factor that may explain the association, between SEP and rates of diagnosis of vitamin D deficiency, is higher overall primary care consultation rates among children from more deprived backgrounds (Saxena et al, 1999).

The magnitude of the effects of ethnicity and SEP were reduced after accounting for clustering by practice. In the multilevel model, rate ratios for the diagnosis of vitamin D deficiency were 8.0 in Asian children (95% CI: 7.0 to 9.1) and 5.5 in black children (95% CI: 4.7 to 6.4), when compared to children from white ethnic backgrounds. The rate ratio in children from the most deprived compared to the least deprived IMD quintile was 2.0 (95% CI: 1.5 to 2.3). One possible explanation for this observation is that the socio-demographic characteristics of a practice population may have contextual effects on clinicians' diagnostic behaviour, separate from the influence of

individual patients' characteristics. GPs working in practices with more deprived and ethnically diverse patient populations may be more likely to test for vitamin D deficiency even in low-risk patients (i.e. independently of the characteristics of individual patients). This could be due to increased awareness and consideration of vitamin D deficiency among GPs working in such areas.

Vitamin D deficiency was diagnosed more frequently in older compared to younger children, and the influence of age was more pronounced in girls compared to boys. The rate ratio for diagnosis in girls aged 15 to 17 years compared to girls aged 0 to 4 years was 8.5 (95% CI: 6.9 to 10.5). In boys, the rate ratio for children aged 15 to 17 compared to those aged 0 to 4 years was 2.4 (95% CI: 1.9 to 3.0). In children aged <5 years, vitamin D deficiency was diagnosed less frequently in girls compared to boys (RR 0.78, 95% CI: 0.64 to 0.97). In older children, diagnosis rates were higher in girls; among children aged 15 to 17 years the rate ratio for diagnosis in girls compared to boys was 2.6 (95% CI: 2.2 to 3.0). One possible explanation for these findings may be that chronic pain and other non-specific or medically unexplained symptoms, which may prompt investigation of vitamin D status, are more frequent among older compared to younger children, and in girls compared to boys (Berntsson & Kohler, 2001; Campo et al, 1999; Eminson et al, 1996; King et al, 2011; Lieb et al, 2000; Vila et al, 2009). Other contributing factors for the sex difference observed in older children may include higher overall primary care consultation rates among girls compared to boys during adolescence (Wang et al, 2013), and the influence of cultural or religious dress in females from certain ethnic or religious groups. The difference in diagnosis rates by age may also be related to higher thresholds for undertaking blood tests in younger children; clinicians may be less likely to request vitamin D tests in younger children with vague or non-specific symptoms, compared to older children.

#### *5.5.1.3 Presenting Symptoms Among Children Diagnosed with Vitamin D Deficiency*

Symptoms and clinical complications that can be caused by vitamin D deficiency were coded in the primary care medical record in a minority (42%) of the children who met the case criteria for diagnosis of vitamin D deficiency. In >90% of these children, a non-specific symptom was recorded (musculoskeletal or non-specific pain, or tiredness / fatigue). There are no previous studies that have investigated the clinical presentation of children diagnosed with vitamin D deficiency in primary care, with which these results can be compared.

### 5.5.2 Study Strengths

THIN is a prospectively collected database of electronic healthcare records from UK primary care. As it contains routine consultation data, it is representative of real life, contemporary clinical practice. The large sample size of the THIN database is a major strength and was necessary for the investigation of the diagnosis of vitamin D deficiency in children, which is a relatively uncommon outcome, and the exploration of associations with socio-demographic characteristics. The longitudinal nature of the data allowed investigation of trends in the diagnosis of vitamin D deficiency in children over time.

The vast majority of the UK population is registered with a general practice, and the THIN cohort has been shown to be broadly representative of the UK population as a whole in terms of age and sex distribution, mortality rates, and the prevalence of various chronic medical conditions (Blak et al, 2011). Furthermore, the recording of consultations and prescriptions in THIN practices is comparable to national primary care statistics (Bourke et al, 2004). Therefore, the results of the study should be broadly generalisable to children in the UK as a whole.

The inclusion of vitamin D prescriptions and tests in the case definition allowed identification of children where the diagnosis of vitamin D deficiency was not recorded using Read codes, for example where the diagnosis may have been entered in free text. Analysis of UK primary care electronic health data has shown that GPs do not always record medical diagnoses using Read codes (Ford et al, 2013). In the present study, the rates of diagnosis of vitamin D deficiency obtained when only diagnosis Read codes were used for case identification were approximately half that observed when all three components of the case definition were used together (see section 5.4.3.2), highlighting the degree of case under-ascertainment that can occur if diagnosis Read codes alone are used to identify cases from primary care data.

Medication prescriptions in primary care are particularly well recorded in THIN, as they are issued electronically by general practitioners (GPs) and automatically captured in the electronic patient record (Thiru et al, 2003). Most THIN practices are electronically linked to pathology laboratories, and the results of tests requested in primary care are sent electronically to the practice and automatically stored in patients' health records (CSDMRUK, 2010). As GPs act as gatekeepers in primary care to secondary healthcare services in the UK, diagnoses made in secondary care can also be captured in THIN, from information contained in discharge summaries and outpatient

letters. Information in patient-related correspondence from secondary care that is deemed to be important may be coded into the primary care electronic health record by GPs themselves or by practice administrative staff. Furthermore, the continuation of medication commenced in secondary care usually requires further prescriptions to be issued in primary care. Therefore, children diagnosed with vitamin D deficiency and started on treatment with calciferol in secondary care may be captured in THIN, if repeat prescriptions required to complete the course of treatment are issued by the GP.

Missing data for ethnicity was substantially reduced by utilising linked HES data, and by linking children to their mothers in the THIN database and taking maternal ethnicity as a proxy measure where the child's ethnicity was not available. Using these methods considerably reduced the proportion of children with missing data for ethnicity in the linked THIN-HES cohort from 57.8% to 18.5%.

### *5.5.3 Study Limitations*

Although the THIN cohort has been shown to be broadly comparable to the UK population as a whole, information regarding the representativeness of the subgroup of the cohort linked to HES data is not available. However, in this study, the full THIN cohort and the linked THIN-HES cohort were similar in terms of distribution of age, sex, ethnicity, and Townsend Index of deprivation.

THIN has been shown to be somewhat under-representative of individuals from the most deprived areas in the country, as measured by the Townsend deprivation index (Blak et al, 2011). This pattern was also observed among children in the study cohort. Given that socio-economic deprivation was positively associated with the diagnosis of vitamin D deficiency, the diagnosis rates observed in the study cohort may underestimate true national rates to an extent.

Although vitamin D prescriptions and tests were included in the case definition to minimise case under-ascertainment, it is possible that some cases may still have been missed. For example, children who were diagnosed and received their full course of treatment in secondary care would have been missed if the diagnosis was not subsequently entered into the primary care record from hospital correspondence. The use of HES data as an additional source of case identification had negligible influence on observed rates of diagnosis. This is likely to be due to the limitation that information regarding clinical diagnoses was only available in HES inpatient data, whilst the

majority of children diagnosed with vitamin D deficiency in secondary care are likely to be identified in the outpatient setting.

Prior to 2013, a Read code for 'Vitamin D insufficiency' was not available, and it is possible that some children in whom a Read code for vitamin D deficiency was recorded may have had serum 25-OH-D levels in the range that is commonly defined as representing insufficiency (25 to 50 nmol/L). However, sensitivity analysis demonstrated that the inclusion of the 'Vitamin D insufficiency' Read code in the case definition had little overall impact (<3% difference) on observed rates of diagnosis of vitamin D deficiency between 2013 to 2014 (see section 5.4.3.4). Some misclassification of case status may also have arisen from assumptions made when coding prescription dosage instructions, and from the choice of dosage thresholds representing 'treatment dose' calciferol in the case definition. However, this is not expected to have had a major overall effect on the results, as dosage assumptions were made in a minority of prescription records (7.9%), and overall time trends in the diagnosis of vitamin D deficiency were similar when a range of alternative dosage thresholds representing 'treatment dose' calciferol were used (the maximal difference in rates across the range of alternatives was <15%, in 2014) (see section 5.4.3.5).

Whilst the accuracy of recorded ethnicity in HES has been shown to be high for patients from white backgrounds, it is less reliable for individuals from ethnic minority groups. Among adults with cancer, concordance between ethnicity recorded in HES with self-reported ethnicity, collected for the English Cancer Patient Experience Survey, has been shown to be very high for patients with ethnicity recorded as 'white' in HES (99.4%), and reasonable for patients with ethnicity recorded as 'Asian or Asian British' (88.9%) or 'black or black British' (84.6%) in HES (Saunders et al, 2013). However, concordance was low for patients with ethnicity recorded as 'Chinese or other ethnic group' (67.0%) or 'mixed' (25.1%) in HES. To date, validation studies have not been conducted to investigate the accuracy of ethnicity data in UK primary care health records. Therefore, particular caution should be used in the interpretation of observed rate ratios for the diagnosis of vitamin D deficiency in the 'mixed' and 'Chinese or other' ethnic groups, among whom the risk of misclassification of ethnicity is likely to be greatest. Whilst the use of maternal ethnicity as a proxy measure for children's ethnicity helped to reduce the extent of missing data for this variable, the risk of misclassification will be greater where maternal ethnicity was used instead of a direct record of ethnicity for the child. However, this is not expected to have had a major impact on the results as, where data was available for both children's and maternal ethnicity, overall agreement between the variables was found to be high (94%).

There was a moderate proportion of missing data for ethnicity (12.7%) and Index of Multiple Deprivation (8.3%) in the multivariable analyses. However, the results were very similar when missing data was handled using complete cases analysis and multiple imputation, suggesting that missing data did not substantially influence the findings under the missing at random assumption (Sterne et al, 2009).

Exploration of presenting symptoms among children diagnosed with vitamin D deficiency was limited by the data available in the primary care electronic record. Only 42% of children meeting the case criteria for diagnosis of vitamin D deficiency had a relevant symptom code recorded in the 6 months either side of their initial diagnosis. One reason for this may be that GPs enter some clinical information as free text rather than using Read codes (Ford et al, 2013). However, exploration of free text entries in the primary care record, for a convenience sample of 55 children diagnosed with vitamin D deficiency, provided additional information regarding presenting symptoms, not already available from Read codes, in only 4 of the children (7.3%). Given the time constraints of consultations in primary care, it is likely that GPs are not able to enter detailed records during consultations, and it is possible that information regarding symptoms that prompted investigation of vitamin D status were not recorded. Furthermore, for children who were diagnosed with vitamin D deficiency in secondary care, it is unlikely that information regarding their clinical presentation will have been recorded in the primary care record. Another explanation for the limited recording of symptoms among cases is likely to be that a proportion of children diagnosed with vitamin D deficiency will have been asymptomatic, with screening of vitamin D status prompted by the presence of risk factors or non-musculoskeletal diseases that have been linked to vitamin D deficiency in observational studies.

### *5.5.4 Conclusions*

There has been a marked increase in the diagnosis of vitamin D deficiency in UK children in clinical practice over the last decade. Given the magnitude of the increase in diagnosis over a relatively short period of time, it is highly unlikely to be explained by changes in population vitamin D levels, incidence of clinical complications of vitamin D deficiency, or population demographics. It is likely that the rise in testing and treatment has been driven by increased awareness and consideration of vitamin D deficiency among clinicians. The data available did not permit meaningful exploration of the clinical indications prompting investigation of vitamin D status. Therefore, it is not clear how much the increase in diagnosis is being driven by improved recognition of children

with clinical features consistent with symptomatic vitamin D deficiency, or by testing in other clinical situations (for example screening of asymptomatic children, testing in children with non-specific symptoms, or testing prompted by the presence of non-musculoskeletal diseases that have been linked to vitamin D deficiency). The implications of the work described in this chapter, with respect to clinical practice, public health policy and future research, are further discussed in the final chapter of the thesis.

Chapter 6

# Costs of Vitamin D Testing and Prescribing Among Children in Primary Care in the UK: A Cohort Study Using Primary Care Electronic Health Records

## 6.1 Introduction

Large increases in healthcare expenditure on vitamin D tests and prescriptions have been reported in adult practice in the UK, Australia, and Canada over the last decade. In the previous chapter, data was presented demonstrating a marked increase in the diagnosis of vitamin D deficiency in clinical practice among children in the UK between 2008 to 2014. This chapter describes a cohort study undertaken to explore the economic implications of this change in diagnostic behaviour, by investigating longitudinal trends in healthcare expenditure arising from vitamin D testing and prescribing among children in primary care in the UK.

## 6.2 Aims and Objectives

### *6.2.1 Study Aims*

The overall aim of this study was to explore longitudinal trends in healthcare expenditure arising from vitamin D testing and prescribing among children in primary care in the UK over the past 15 years.

### *6.2.2 Study Objectives*

i) To determine healthcare costs in primary care in the UK arising from calciferol prescriptions and 25-hydroxyvitamin D (25-OH-D) tests for children, in each year between 2000 and 2014.

ii) To estimate overall costs of calciferol prescriptions and 25-OH-D tests for children in primary care at the national level in England.

## 6.3 Methods

### *6.3.1 Study Design*

A cohort study using UK primary care electronic health records, held in The Health Improvement Network (THIN) database.

### *6.3.2 Data Sources*

The Health Improvement Network database has been described in chapter 5.3.2.1. The February 2015 release of THIN data was used for the analysis reported in this chapter, containing primary care medical records for 11.6 million patients in total, registered with 641 general practices in the UK, from 3rd June 1985 up to 10th February 2015. Linked Hospital Episode Statistics (HES) data was used to augment information regarding ethnicity. This was available for a subset of THIN practices in England (n=156), covering the time period 1st April 1997 to 31st March 2012, and has been described in chapter 5.3.2.2.

### *6.3.3 Study Population*

#### *6.3.3.1 Inclusion and Exclusion Criteria*

The study population included children aged between 0 to 17 years, who were actively registered with a THIN practice between 1st January 2000 and 31st December 2014. Only individuals with an acceptable patient record status (Patflag A or C) were included (see chapter 5.3.3.1). Children with a record of a medical condition that can predispose to vitamin D deficiency by interfering with vitamin D absorption or metabolism (chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption; see chapter 5.3.6.8) were excluded, as routine screening of vitamin D status is expected in children with these conditions.

The full THIN study cohort was used for the main analysis of time-trends in healthcare costs arising from calciferol prescriptions and 25-OH-D tests among children in primary care. For the extrapolation of national cost estimates from costs observed in the cohort,

the analysis was limited to THIN practices for which linked HES data was available (the linked THIN-HES study cohort), in order to minimise missing data for ethnicity (see chapter 5.4.2, and section 6.3.6.2).

#### *6.3.3.2 Entry to Study Observation Period*

The study cohort was open (dynamic), meaning that children entered and exited the cohort at different time points. Therefore, they were observed over different periods of time, and contributed different lengths of follow-up to the study.

The date of entry into the cohort for each individual, i.e. the start of their period of observation (follow-up), was set as the latest of the following dates:

i) Start of the study period (1st January 2000).

ii) Date of registration with the GP practice.

iii) The date when the practice met pre-defined criteria for acceptable mortality recording (AMR date, see chapter 5.3.3.2).

iv) The date when the practice met pre-defined criteria for acceptable computer usage (ACU date, see chapter 5.3.3.2).

#### *6.3.3.2 Exit from Study Observation Period*

The date of exit from the cohort for each individual was set as the earliest of the following dates:

i) Mid-point of 18th year after birth.

ii) Date of transfer out of the practice.

iii) Date when the practice stopped contributing data to THIN.

iv) Date of death.

v) End of the study period (31st December 2014).

The mid-point of the 18th year after birth was used, as opposed to the 18th birthday, because exact dates of birth are not provided in THIN in order to protect patient

confidentiality. Month of birth is provided for children below 15 years of age at the time of the data release, whilst for older individuals only year of birth is available.

### *6.3.4 Outcome*

The primary outcome was the cost arising from calciferol prescriptions and 25-OH-D tests in primary care among children in the study cohort.

#### *6.3.4.1 Identification of Calciferol Prescriptions and 25-OH-D Tests*

All prescriptions for pure preparations of calciferol (colecalciferol or ergocalciferol) were included. Activated analogues of vitamin D, such as alfacalcidol and calcitriol, were not included as these are not routinely recommended for the treatment of primary vitamin D deficiency, and are generally used in situations where vitamin D metabolism is impaired (e.g. chronic renal impairment) or in hypoparathyroidism (see chapter 2.3.3). The strategy used for identification of drug codes referring to pure preparations of calciferol is described in chapter 5.3.6.4, and the final list of included codes is shown in Appendix G.1.

The strategy used for identification of Read codes referring to vitamin D tests, along with the final list of included codes, is described in chapter 5.3.6.5. Codes referring to levels of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, combined total 25-hydroxyvitamin D2 and D3, 25-hydroxyvitamin D (type not specified), and unspecified vitamin D were included. The distribution of test values for the unspecified vitamin D tests was similar to that for vitamin D3 tests and total vitamin D2 & D3 tests (see chapter 5.3.7.2). Therefore, unspecified vitamin D tests were considered to represent measurement of either 25-hydroxyvitamin D3 or total 25-hydroxyvitamin D2 & D3. Codes referring to 1,25-dihydroxyvitamin D tests were excluded, as levels of the biologically active hormone are not used to assess an individual's vitamin D status.

For the purpose of this study, the outcome of interest was total healthcare expenditure on vitamin D testing and prescribing for children in primary care. Therefore, distinction was not made between 'prophylactic' and 'treatment' dosage, and all prescriptions of calciferol were included irrespective of dosage. Similarly, all records representing 25-OH-D tests were included, irrespective of the value of the test result.

Where individuals had more than one vitamin D test code recorded on the same date (for example separate codes for levels of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, and combined total 25-hydroxyvitamin D2 and D3), this was taken to represent a single 25-OH-D test.

#### *6.3.4.2 Unit Cost of 25-OH-D Tests*

In an economic evaluation commissioned by the National Institute for Health and Care Excellence (NICE), a unit cost for vitamin D tests was derived from information contained in local clinical guidelines published by two NHS trusts (Filby et al, 2014); The Royal National Orthopaedic Hospital gave a unit cost of £20 (Jacobs, 2013), and a statement from NHS Derby City and NHS Derbyshire County reported a cost of £13 (Filby et al, 2014).

A search was conducted on 2nd February 2016 to identify any further data published by NHS trusts regarding the unit cost of vitamin D tests. Three additional clinical guidelines, and one service tariff, were identified. Clinical guidelines published by the Nottinghamshire Area Prescribing Committee (Prinsloo et al, 2015), and NHS Forth Valley (Allan et al, 2015), reported the unit cost of a 25-OH-D test to be £15. A provider to provider services tariff from University College London Hospitals NHS Foundation Trust also reported a unit cost for 25-OH-D tests of £15 (UCLH, 2012). A clinical guideline published by the NHS Wandsworth Clinical Effectiveness and Medicines Management Group reported the unit cost of a 25-OH-D test to be £15.61 (Wouda, 2010).

The unit cost of a 25-OH-D test was taken as £15 for the main analyses, as this was the most frequently reported value in the sources of information identified above. A sensitivity analysis was performed to explore the influence on the results of varying the 25-OH-D test unit cost between £13 to £20.

#### *6.3.4.3 Unit Costs of Calciferol Preparations*

Unit costs for the different preparations of pure calciferol, identified in the THIN drug code dictionary (see appendix G.1), were derived from Prescription Cost Analysis (PCA) for England 2014 data (HSCIC, 2015b). PCA data is published by NHS Digital (formerly known as the Health and Social Care Information Centre [HSCIC]), and contains details of all NHS prescriptions dispensed in the community (by community

pharmacies or dispensing doctors) in England in each year. For every drug, PCA data includes information regarding the number of items (prescriptions) dispensed, quantity of drug dispensed (measured in units depending on the form of the drug, e.g. tablets, capsules, millilitres), and the total net ingredient cost (NIC) for all prescriptions of the drug. The NIC refers to the cost of the drug before discounts, and does not include any dispensing costs or fees. The NIC is generally equivalent to the NHS indicative price listed in the British National Formulary (BNF). The average NIC per item (prescription), and the average NIC per quantity of drug (NIC/Qty) have been derived and are available in the PCA data.

For each drug or chemical entity, the PCA lists all forms (e.g. tablets, capsules, liquid) and strengths of the drug. For each form and strength of a drug, all proprietary (branded) and generic names under which the drug is sold are listed. In contrast, proprietary names of prescribed drugs are not made available in THIN. THIN drug codes are linked to a description of the drug's generic name only, as well its form and strength. Therefore, there can be multiple drugs listed in the PCA corresponding to each THIN drug code. An example is shown in Table 6.1.

For each THIN drug code, a unit cost was calculated representing the cost (in £) per quantity of the drug (i.e. per tablet, capsule, or millilitre). For THIN drug codes corresponding to a single drug entry in the PCA, the NIC/Qty in the PCA was taken to represent the unit cost of the drug. In the case of THIN drug codes corresponding to multiple different drugs (with identical form and strength) listed in the PCA, a weighted mean unit cost was calculated using the NIC/Qty, with weighting by the relative frequency with which each drug was dispensed in 2014, as shown below:

$$Weighted\ unit\ cost\ = \frac{\sum_i (NIC\_Qty_i\ \times\ N_i)}{\sum_i N_i}$$

*Key:* $i$*: each drug listed in the PCA corresponding to the same THIN drug code*
*NIC_Qty: the net ingredient cost per quantity (e.g. tablet or ml) of the drug*
$N$*: the total number of items (prescriptions) of each drug dispensed in* 2014

An example of the calculation of weighted unit cost for a THIN drug code is shown in Table 6.1.

**Table 6.1** An example of the calculation of the weighted unit cost for a THIN drug code that has more than one corresponding drug listed in the PCA.

| THIN drug code description | Variables from Prescription Cost Analysis | | | | Derived variables | |
|---|---|---|---|---|---|---|
| | **Drug Name** (*i*) | **NIC_Qty** (£ / ml) | **Items dispensed** (*N*) (1,000s) | **Total items** ($\sum N$) (1,000s) | **Weight** ($N / \sum N$) | **Weighted unit cost** (£ / ml) [a] |
| Colecalciferol 2,000units/ml oral drops sugar free | Colecal_Oral Dps 2,000u/ml S/F | 2.64 | 0.638 | 11.945 | 0.0534 | 0.65 |
| | E-D3_Oral Dps 2,000u/ml | 4.99 | 0.118 | 11.945 | 0.0099 | 0.65 |
| | Pro D3_Oral Dps 2,000u/ml | 0.49 | 11.189 | 11.945 | 0.9367 | 0.65 |

Abbreviations: NIC_Qty, net ingredient cost per quantity of drug.
[a] The weighted unit cost is calculated as follows: $\sum_i$ (NIC_Qty x weight).

Unit costs were kept constant over time, so that analysis of time-trends in expenditure represented changes in levels of healthcare activity over time rather than changes in the monetary value of drugs. 2014 was chosen as the index (base) year for costs, as this was the most recent year for which follow-up data was available for the study.

#### *6.3.4.4 Calculation of Costs of Individual Prescriptions*

The cost of each prescription of pure calciferol recorded in the study cohort was calculated by multiplying the weighted unit cost of the drug by the quantity prescribed. For most records, the variable for 'quantity prescribed' in the THIN prescription record represents the amount of the drug prescribed in terms of units of measurement of the form of the drug (e.g. tablets, capsules, millilitres). However, in a minority of prescription records the variable 'quantity prescribed' represents the number of 'packs' of the drug prescribed. A 'pack' can represent, for example, a packet of tablets, or a bottle of liquid medication. Therefore, for each THIN drug code separately, the distribution of the variable 'quantity prescribed' was examined for all prescriptions of the drug in the study cohort, in order to identify low value outliers likely to represent the number of packs prescribed as opposed to the quantity of drug prescribed. An example is shown in Table 6.2.

**Table 6.2** Distribution of the variable 'quantity prescribed' for prescriptions of the THIN drug code for 'Colecalciferol 3,000units/ml oral solution sugar free'.

| Quantity prescribed | Frequency (N = 240) | Percentage |
|---|---|---|
| 1 | 1 | 0.42 |
| 20 | 1 | 0.42 |
| 28 | 2 | 0.83 |
| 30 | 41 | 17.1 |
| 50 | 122 | 50.8 |
| 60 | 20 | 8.3 |
| 100 | 31 | 12.9 |
| 120 | 1 | 0.42 |
| 150 | 4 | 1.7 |
| 180 | 1 | 0.42 |
| 200 | 15 | 6.3 |
| 300 | 1 | 0.42 |

In the example shown in Table 6.2, the prescription record for 'Colecalciferol 3,000units/ml oral solution sugar free' with a 'quantity prescribed' of 1 was considered to represent a low value outlier, where the 'quantity prescribed' was likely to represent the number of packs prescribed. For such prescription records, where the 'quantity prescribed' was considered to be a low value outlier, the value of the variable was replaced using the mode value from the distribution of the variable for all prescriptions of the same drug code (i.e. the most frequently recorded 'quantity prescribed' for prescriptions of the identical drug). In the case of the example shown in Table 6.2, for the prescription record for 'Colecalciferol 3,000units/ml oral solution sugar free' with the 'quantity prescribed' recorded as 1, the value of this variable was replaced with 50.

For high strength preparations of calciferol, defined as ≥10,000 units per dosage unit (i.e. tablet or ml), exploration of dosage instructions linked to prescriptions with low values (<5) for the 'quantity prescribed' revealed that many such prescriptions were linked to dosage instructions specifying infrequent administration (e.g. once monthly, or once weekly). In such cases, the 'quantity prescribed' was considered likely to represent the amount of the drug prescribed in terms of units of measurement of the form of the drug (e.g. tablets, capsules, millilitres), rather than number of packs. Therefore, for preparations of calciferol with a strength ≥10,000 units per dosage unit, low values for 'quantity prescribed' were not considered to represent outliers, and the original values were retained when calculating costs of prescriptions.

In cases where individuals had more than one prescription for calciferol issued on the same day, the cost of all prescriptions issued on that date were summed and considered to represent a single prescription, for the purpose of calculation of mean prescription costs (see section 6.3.6.1).

### *6.3.5 Covariates*

The following study covariates were used to stratify observed costs in the study cohort: sex, age, and ethnicity. The methods for handling and coding data for the study covariates is described in chapter 5.3.5.

### *6.3.6 Statistical Analysis*

All statistical and graphical analyses were performed using Stata MP version 14.2 (StataCorp, USA).

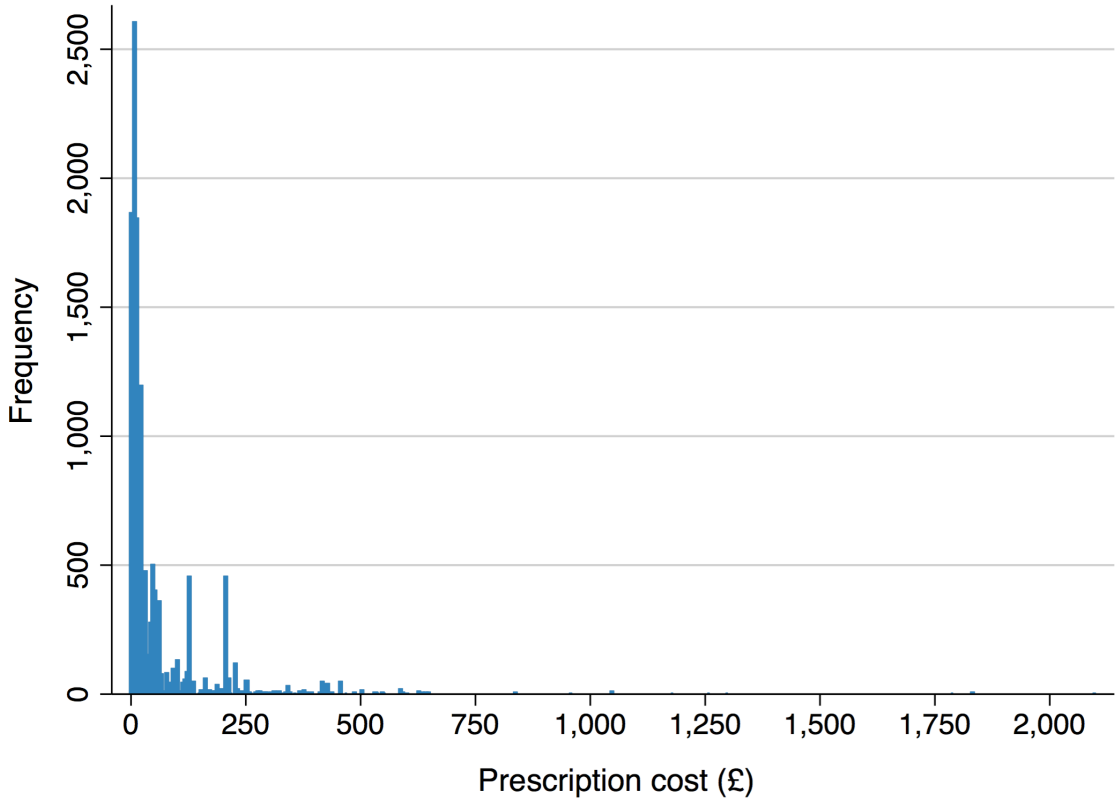
#### *6.3.6.1 Analysis of Time Trends in Costs of Vitamin D Testing and Prescribing in the Study Cohort*

Crude rates for 25-OH-D tests and calciferol prescriptions in the cohort were calculated separately, per 100,000 person-years at risk (PYAR), using the *stset and strate* functions in Stata. All test and prescription records for each individual were included in the analysis. Multiple test, or prescription, records on the same date for an individual were considered to represent a single event. In order to explore incidence rates stratified by time-changing variables (age and calendar time), Lexis expansions were used to divide individuals' follow-up into distinct categories of the time-changing variables, using the *stsplit* function in Stata (Kirkwood & Sterne, 2003). Calendar time was split into individual years, between 2000 to 2014.

Mean costs of calciferol prescriptions in each year between 2000 and 2014 were calculated, using bootstrapping to derive confidence intervals as the distribution of prescription costs was severely positively skewed (Figure 6.1). The bootstrap approach is a non-parametric method that makes very limited distributional assumptions concerning the statistic in question, and is recommended as an appropriate method for handling sampling uncertainty in healthcare cost data which often follows a skewed

distribution (Briggs & Gray, 1999; Desgagne et al, 1998; Thompson & Barber, 2000). The *bootstrap* function in Stata was used to re-sample observations (with replacement) from the original sample of prescription costs in each year, to generate 10,000 re-sampled datasets. The percentile method was used to calculate confidence intervals from the resampled datasets (Kirkwood & Sterne, 2003). Using this method, the 95% confidence interval for the mean prescription cost in each year was derived from the 2.5$^{th}$ and 97.5$^{th}$ percentile values from the distribution of mean prescription costs from the re-sampled datasets. A sensitivity analysis was performed to explore the influence of using the alternative bias-corrected and accelerated (BCa) method for deriving bootstrap confidence intervals (Kirkwood & Sterne, 2003).

**Figure 6.1** Distribution of the cost of calciferol prescriptions in the study cohort.




Total costs of 25-OH-D tests in each year were calculated per 100,000 PYAR, by multiplying rates of testing in each year by the unit cost of a 25-OH-D test (£15 for the main analysis). 95% confidence intervals around these cost estimates were calculated by multiplying the 95% confidence limits for the rates of testing in each year by the unit cost of a 25-OH-D test.

Total costs of calciferol prescriptions in each year were calculated per 100,000 PYAR, by multiplying rates of prescribing in each year by the mean prescription cost in the corresponding year. 95% confidence intervals around these cost estimates were calculated by multiplying the lower (and upper) 95% confidence limit for the rate of prescribing in each year by the lower (and upper) 95% confidence limit for the mean prescription cost in the corresponding year.

#### *6.3.6.2 Extrapolation of National Cost Estimates*

Overall costs of calciferol prescriptions and 25-OH-D tests for children in primary care were estimated at the national level for England in 2014. Stratified rates of expenditure observed in the linked THIN-HES study cohort were applied to 2014 population estimates for England. This analysis involved the following steps:

i) Observed rates of calciferol prescription and 25-OH-D testing in the linked THIN-HES study cohort in 2014 were stratified by age group, sex, and ethnicity, using the *stsplit* and *strate* functions in Stata.

ii) Variation in the cost of vitamin D prescriptions, issued in the linked THIN-HES study cohort in 2014, was explored by age group, sex, and ethnicity. Multivariable generalised linear models were used in view of the highly-skewed distribution of the data (Barber & Thompson, 2004), using the *glm* function in Stata. Models with a gamma distribution function were found to provide a better fit for the data compared to models specifying an inverse Gaussian or Gaussian distribution (as assessed using residual plots and the Akaike information criterion). However, even with the gamma distribution function, the histogram of residuals was not normally distributed and the normal probability plot of the residuals was not straight (Barber & Thompson, 2004). Therefore, the distributional assumptions of the model were relaxed using robust standard errors.

   Significant variation in prescription costs was observed by age group, however there were no significant differences observed by sex or ethnicity (Table 6.3). Therefore, age group specific mean calciferol prescription costs were derived using a generalised linear model (with gamma distribution function, log link function, and robust standard errors) which included only age group as an explanatory variable (Table 6.4).

**Table 6.3** Associations between selected demographic factors and calciferol prescription costs.[a]

| Covariate | Regression coefficient (95% CI) [b] | p-value [c] |
|---|---|---|
| *Sex* | | 0.366 |
| Male | Baseline | |
| Female | 0.92 (0.77–1.10) | |
| *Age group* | | <0.001 |
| 0 – 4 years | Baseline | |
| 5 – 9 years | 0.84 (0.68–1.03) | |
| 10 – 14 years | 0.39 (0.31–0.49) | |
| 15 – 17 years | 0.29 (0.23–0.37) | |
| *Ethnicity* | | 0.708 |
| White | Baseline | |
| Asian or Asian British | 0.88 (0.72–1.07) | |
| Black or black British | 0.95 (0.74–1.21) | |
| Mixed | 0.93 (0.71–1.21) | |
| Chinese or other ethnic group | 0.88 (0.68–1.13) | |
| *Constant (£)* | 63.7 (51.8–78.4) | - |

Abbreviations: CI, confidence interval

[a] The analysis included all prescriptions of calciferol issued in 2014 in the linked THIN-HES study cohort. Missing data for ethnicity was handled using complete cases analysis. N=1,428.

[b] Exponentiated regression coefficients from a multivariable generalised linear model with gamma distribution function, log link function, and robust standard errors. The model adjusted for all variables listed in the table. In this model covariates act multiplicatively on the mean, and the exponentiated regression coefficients therefore represent the relative difference in mean prescription costs between categories of the covariates.

[c] p-values from Wald tests of the overall association between each variable and prescription costs.

**Table 6.4** Predicted mean calciferol prescription costs for each age group category.[a]

| Age group | Mean Prescription Cost (£) [b] | 95% CI (£) |
|---|---|---|
| 0 – 4 years | 57.3 | 48.3–66.3 |
| 5 – 9 years | 47.9 | 41.8–54.0 |
| 10 – 14 years | 22.6 | 19.4–25.8 |
| 15 – 17 years | 16.3 | 13.9–18.6 |

Abbreviations: CI, confidence interval

[a] The analysis included all prescriptions of calciferol issued in 2014 in the linked THIN-HES study cohort. N=1,542.

[b] Predicted margins from a generalised linear model with gamma distribution function, log link function, and robust standard errors. The model included age group as the only independent variable.

iii) Rates of vitamin D testing in each of the cohort strata (defined by age group, sex, and ethnicity) were multiplied by the unit cost of a 25-OH-D test (£15), to derive stratum-specific costs of vitamin D testing per 100,000 PYAR. 95% confidence intervals around the stratum specific cost estimates were calculated by multiplying the 95% confidence limits for the rates of testing in each stratum by the unit cost of a 25-OH-D test.

iv) Rates of vitamin D prescribing in each of the cohort strata were multiplied by age-specific unit costs of calciferol prescriptions (Table 6.4), to derive stratum specific costs of vitamin D prescribing per 100,000 PYAR. 95% confidence intervals around the stratum specific cost estimates were calculated by multiplying the lower (and upper) 95% confidence limits for the rate of prescribing in each stratum by the lower (and upper) 95% confidence limits for the mean prescription cost for the corresponding age group.

v) 2014 population estimates for children in England, stratified by age group and sex, were available from the Office for National Statistics (ONS) (ONS, 2015). However, population estimates stratified by ethnicity were not available for 2014. The ethnicity distribution of children in the 2011 census was calculated (ONS, 2013a), separately for strata defined by age group and sex. The strata-specific ethnicity distributions from 2011 were then applied to 2014 population estimates stratified by age group and sex, to derive population estimates for 2014 stratified by age group, sex, and ethnicity.

vi) Stratum-specific rates of expenditure for vitamin D testing and prescribing observed in the study cohort (derived in steps iii and iv) were applied to 2014 population estimates stratified by age group, sex, and ethnicity (derived in step v), in order to derive estimated costs in each population stratum in England in 2014. Stratum specific costs were summed to derive total estimated costs of vitamin D testing and prescribing in England in 2014.

### *6.3.7 Ethical Approval*

The ethical approval for this study is described in chapter 5.3.9.

## 6.4 Results

### *6.4.1 Descriptive Characteristics of the Study Cohort*

#### *6.4.1.1 Full THIN Study Cohort*

The full study cohort consisted of 2,372,913 children, from 639 general practices, with a total period of follow-up of 11.7 million person-years. Median duration of study follow-up was 3.7 years per individual (IQR 1.5 to 7.7). 11,974 children with a record of either chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption, were excluded from the study cohort. Descriptive characteristics of the study population are shown in Table 6.5.

There were a total of 17,719 vitamin D test records, among 13,498 children in the full study cohort, during the period of follow-up. There were a total of 13,664 calciferol prescription records, among 6,168 children in the cohort, during the period of follow-up. It was possible to derive the prescription cost for 13,661 of the prescriptions (>99.9%).

#### *6.4.1.2 Study Cohort with Linked HES Data Available*

When the analysis was limited to children registered with one of the 156 THIN practices in England for which linked HES data was available, the study cohort consisted of 722,525 children, with a total period of follow-up of 3.7 million person-years. Median duration of study follow-up was 3.9 years per individual (IQR 1.5 to 8.1). 3,918 children with a record of either chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption, were excluded from the study cohort. Descriptive characteristics of the linked THIN-HES study population are shown in Table 6.6. Ethnicity was directly available for 67.6% of children in the cohort, and maternal ethnicity was available as a proxy measure of children's ethnicity for a further 14.0% of the cohort. Ethnicity was missing for 18.4% of the study cohort.

There were a total of 7,029 vitamin D test records, among 5,338 children in the linked THIN-HES study cohort, during the period of follow-up. There were a total of 4,586 calciferol prescription records, among 2,272 children in the cohort, during the period of follow-up. It was possible to derive the prescription cost for all of these prescriptions.

**Table 6.5** Descriptive characteristics of the full study cohort (n=2,372,913).

| **Age at entry to follow-up (years)** | **Median (IQR)** |
|---|---|
| | 4.5 (0.16–10.6) |
| **Sex** | **n (%)** |
| Male | 1,223,081 (51.5%) |
| Female | 1,149,832 (48.5%) |
| **Ethnicity** [a] | **n (%)** |
| White | 956,325 (40.3%) |
| Asian or Asian British | 77,139 (3.3%) |
| Black or black British | 51,651 (2.2%) |
| Mixed | 31,512 (1.3%) |
| Chinese or other ethnic group | 29,711 (1.3%) |
| *Missing* | *1,226,575 (51.7%)* |
| **Townsend deprivation index quintile** | **n (%)** |
| 1 (least deprived) | 501,883 (21.2%) |
| 2 | 435,299 (18.3%) |
| 3 | 473,402 (20.0%) |
| 4 | 462,823 (19.5%) |
| 5 (most deprived) | 351,383 (14.8%) |
| *Missing* | *148,123 (6.2%)* |
| **Country, and strategic health authority in England** | **n (%)** |
| England | 1,855,456 (78.2%) |
| *South Central* | *273,327 (11.5%)* |
| *London* | *259,487 (10.9%)* |
| *South East Coast* | *214,224 (9.0%)* |
| *South West* | *211,115 (8.9%)* |
| *North West* | *202,768 (8.6%)* |
| *West Midlands* | *197,903 (8.3%)* |
| *East of England* | *155,625 (6.6%)* |
| *East Midlands* | *75,823 (3.2%)* |
| *Yorkshire & Humber* | *70,725 (3.0%)* |
| *North East* | *53,031 (2.2%)* |
| *Missing* | *141,428 (6.0%)* |
| Scotland | 273,400 (11.5%) |
| Wales | 166,746 (7.0%) |
| Northern Ireland | 77,311 (3.3%) |

Abbreviations: IQR, interquartile range.

[a] Ethnicity data was available from the child's THIN record for 40.1% of the cohort, and maternal ethnicity was available as a proxy measure for a further 8.2%.

**Table 6.6** Descriptive characteristics of the THIN-HES linked study cohort (n=722,525).

| **Age at entry to follow-up (years)** | **Median (IQR)** |
|---|---|
| | 3.9 (0.15–10.5) |
| **Sex** | **n (%)** |
| Male | 371,835 (51.5%) |
| Female | 350,690 (48.5%) |
| **Ethnicity** [a] | **n (%)** |
| White | 499,132 (69.1%) |
| Asian or Asian British | 35,322 (4.9%) |
| Black or black British | 25,315 (3.5%) |
| Mixed | 15,886 (2.2%) |
| Chinese or other ethnic group | 13,712 (1.9%) |
| *Missing* | *133,158 (18.4%)* |
| **Townsend deprivation index quintile** | **n (%)** |
| 1 (least deprived) | 173,445 (24.0%) |
| 2 | 130,713 (18.1%) |
| 3 | 150,717 (20.9%) |
| 4 | 143,669 (19.9%) |
| 5 (most deprived) | 92,500 (12.8%) |
| *Missing* | *31,481 (4.4%)* |
| **Strategic health authority** | **n (%)** |
| South Central | 160,925 (22.3%) |
| South West | 113,327 (15.7%) |
| London | 102,482 (14.2%) |
| South East Coast | 92,871 (12.9%) |
| West Midlands | 91,336 (12.6%) |
| North West | 65,080 (9.0%) |
| East of England | 58,829 (8.1%) |
| North East | 18,805 (2.6%) |
| Yorkshire & Humber | 14,406 (2.0%) |
| East Midlands | 4,464 (0.6%) |

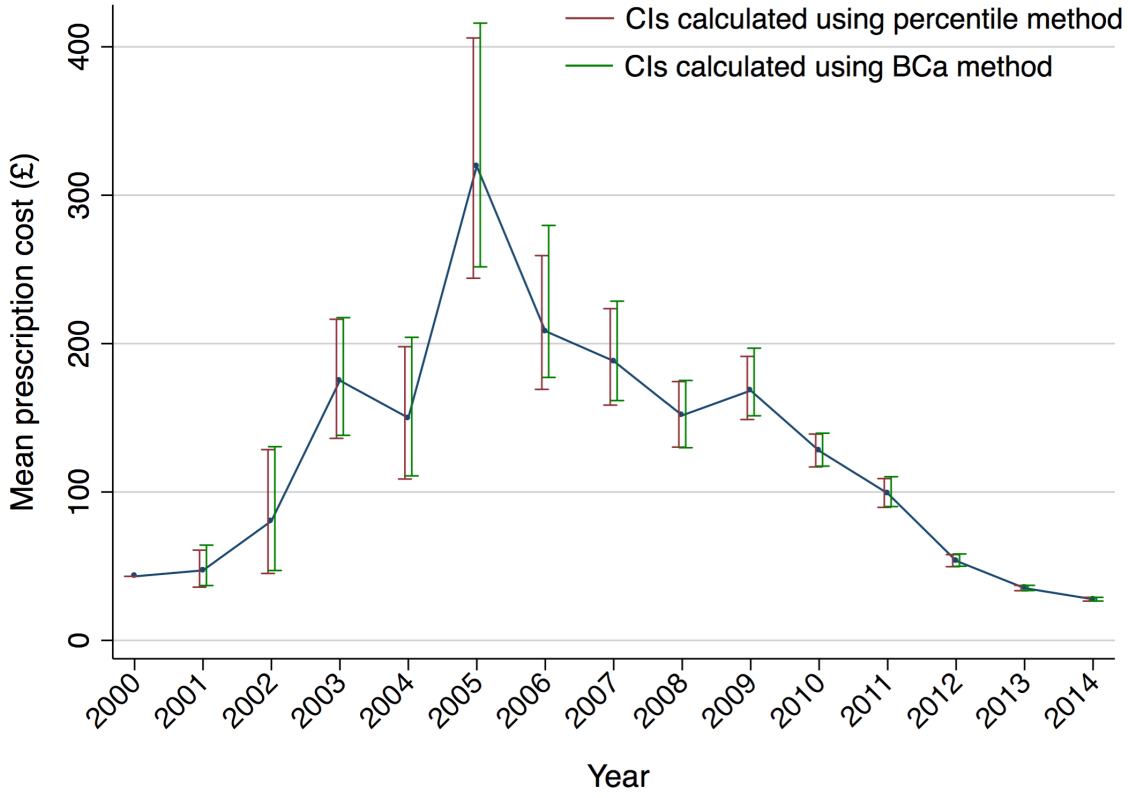
Abbreviations: IQR, interquartile range.

[a] Ethnicity data was available from the child's THIN or HES record for 67.6% of the cohort, and maternal ethnicity was available as a proxy measure for a further 14.0%.

### 6.4.2 Variation in Calciferol Prescription Costs Over Time

Mean costs of calciferol prescriptions in the full THIN study cohort, in each year between 2000 and 2014, are shown in Figure 6.2 and Table 6.7. Mean prescription costs peaked in 2005, then decreased considerably between 2005 to 2014. 95% confidence intervals around mean prescription costs were similar whether the percentile method or the bias-corrected and accelerated (BCa) method for deriving bootstrap confidence intervals were used. Bootstrap confidence intervals derived using the percentile method were used for all further analyses.

**Figure 6.2** Mean calciferol prescription costs in each year between 2000 and 2014, using two alternative methods for deriving bootstrap 95% confidence intervals.[a]




Abbreviations: BCa, bias-corrected and accelerated; CIs, confidence intervals.
[a] 95% confidence intervals calculated using the percentile method for deriving bootstrap CIs are represented by red vertical lines. 95% confidence intervals calculated using the bias-corrected and accelerated method for deriving bootstrap CIs are represented by green vertical lines.

**Table 6.7** Mean calciferol prescription costs in each year between 2000 and 2014, using two alternative methods for deriving bootstrap 95% confidence intervals.

| Year | Number of calciferol prescriptions | Mean prescription cost (£) | 95% CI derived using the percentile method (£) | 95% CI derived using the BCa method (£) |
|---|---|---|---|---|
| 2000 | 6 | 43.1 | 43.1 – 43.1 | - |
| 2001 | 10 | 47.2 | 35.9 – 60.8 | 37.0 – 64.2 |
| 2002 | 10 | 80.5 | 45.1 – 128.5 | 47.1 – 130.5 |
| 2003 | 33 | 175.1 | 136.1 – 216.4 | 138.2 – 217.5 |
| 2004 | 26 | 150.0 | 108.7 – 197.9 | 110.9 – 204.2 |
| 2005 | 52 | 319.5 | 244.0 – 406.0 | 251.7 – 415.9 |
| 2006 | 56 | 208.4 | 169.2 – 259.3 | 177.2 – 279.6 |
| 2007 | 82 | 188.3 | 158.5 – 223.6 | 161.6 – 228.6 |
| 2008 | 98 | 151.6 | 130.3 – 174.4 | 129.8 – 175.2 |
| 2009 | 283 | 168.3 | 148.8 – 191.4 | 151.4 – 196.9 |
| 2010 | 452 | 127.8 | 116.9 – 139.0 | 117.4 – 139.6 |
| 2011 | 865 | 99.1 | 89.6 – 109.0 | 90.2 – 110.3 |
| 2012 | 2,295 | 53.6 | 49.7 – 57.8 | 49.9 – 58.2 |
| 2013 | 4,379 | 35.2 | 33.5 – 37.0 | 33.6 – 37.1 |
| 2014 | 5,014 | 27.7 | 26.5 – 29.0 | 26.5 – 29.0 |

Abbreviations: BCa, bias-corrected and accelerated; CI, confidence interval.

### *6.4.3 Time Trends in Healthcare Expenditure on Vitamin D Testing and Prescribing among Children in Primary Care*

#### *6.4.3.1 Main Results Using the Full THIN Study Cohort*

Analysis of time trends showed a marked increase in healthcare costs arising from both vitamin D prescriptions and tests among children in the full study cohort after 2008 (Table 6.8 and Figure 6.3). The combined cost of calciferol prescriptions and 25-OH-D tests increased from £2,101 per 100,000 person-years in 2008 (95% CI: £1,559 to £2,828) to £28,004 per 100,000 person-years in 2014 (95% CI: £26,465 to £29,640).

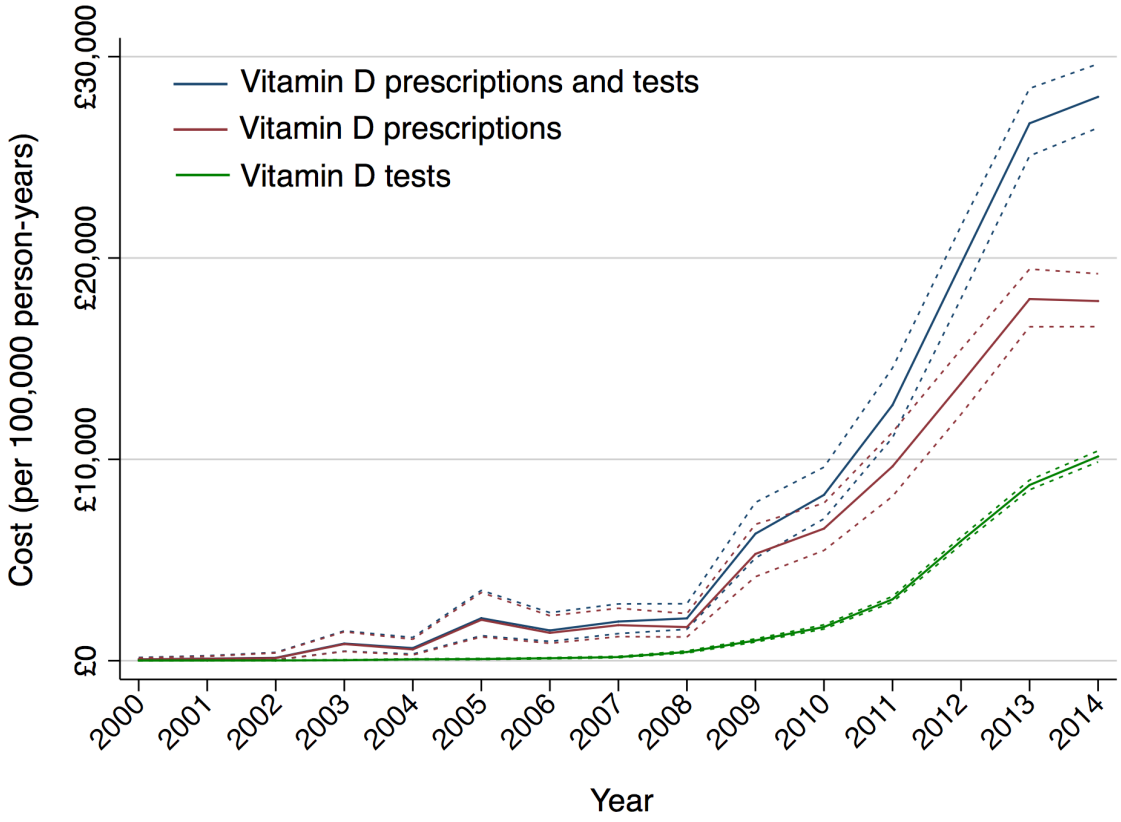
Liquid formulations of calciferol accounted for 35% of prescriptions, and 76% of prescription costs. The majority of calciferol prescriptions (70%, accounting for 75% of prescription costs) were for doses higher than those recommended for prophylactic supplementation or maintenance therapy (>1,000 international units per day).

**Table 6.8** Costs of vitamin D prescriptions and tests among children in the full study cohort, in each year between 2000 to 2014.

| Year | PY of follow-up | Calciferol Prescriptions | | | | 25-OH-D Tests | | | Combined cost of prescriptions & tests per 100,000 PY, £ (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | n | Rate per 100,000 PY (95% CI) | Mean prescription cost, £ (95% CI)[a] | Cost per 100,000 PY, £ (95% CI) | n | Rate per 100,000 PY (95% CI) | Cost per 100,000 PY, £ (95% CI) [b] | |
| 2000 | 437,455 | 6 | 1.37 (0.62–3.05) | 43.1 (43.1–43.1) | 59.1 (26.6–132) | 2 | 0.46 (0.11–1.83) | 6.86 (1.72–27.4) | 66.0 (28.3–159) |
| 2001 | 523,589 | 10 | 1.91 (1.03–3.55) | 47.2 (35.9–60.8) | 90.1 (36.9–216) | 4 | 0.76 (0.29–2.04) | 11.5 (4.30–30.5) | 102 (41.2–246) |
| 2002 | 624,080 | 10 | 1.60 (0.86–2.98) | 80.5 (45.1–129) | 129 (38.9–383) | 5 | 0.80 (0.33–1.92) | 12.0 (5.00–28.9) | 141 (43.9–412) |
| 2003 | 699,008 | 33 | 4.72 (3.36–6.64) | 175 (136–216) | 827 (457–1,437) | 12 | 1.72 (0.97–3.02) | 25.8 (14.6–45.3) | 852 (472–1,482) |
| 2004 | 778,142 | 29 | 3.73 (2.59–5.36) | 150 (109–198) | 559 (282–1,061) | 34 | 4.37 (3.12–6.12) | 65.5 (46.8–91.7) | 624 (328–1,153) |
| 2005 | 818,284 | 52 | 6.35 (4.84–8.34) | 319 (244–406) | 2,030 (1,182–3,386) | 44 | 5.38 (4.00–7.23) | 80.7 (60.0–108) | 2,111 (1,242–3,494) |
| 2006 | 845,216 | 56 | 6.63 (5.10–8.61) | 208 (169–259) | 1,381 (862–2,233) | 68 | 8.05 (6.34–10.2) | 121 (95.2–153) | 1,502 (958–2,386) |
| 2007 | 874,533 | 82 | 9.38 (7.55–11.6) | 188 (159–224) | 1,765 (1,197–2,603) | 105 | 12.0 (9.92–14.5) | 180 (149–218) | 1,945 (1,346–2,821) |
| 2008 | 890,603 | 98 | 11.0 (9.03–13.4) | 152 (130–174) | 1,669 (1,176–2,339) | 257 | 28.9 (25.5–32.6) | 433 (383–489) | 2,101 (1,559–2,828) |
| 2009 | 898,407 | 283 | 31.5 (28.0–35.4) | 168 (149–191) | 5,303 (4,172–6,774) | 601 | 66.9 (61.8–72.5) | 1,003 (926–1,087) | 6,306 (5,099–7,860) |
| 2010 | 880,419 | 452 | 51.3 (46.8–56.3) | 128 (117–139) | 6,561 (5,473–7,826) | 983 | 112 (105–119) | 1,675 (1,573–1,783) | 8,235 (7,047–9,609) |
| 2011 | 888,296 | 865 | 97.4 (91.1–104) | 99.1 (89.6–109) | 9,649 (8,167–11,349) | 1,805 | 203 (194–213) | 3,048 (2,911–3,192) | 12,697 (11,077–14,541) |
| 2012 | 894,047 | 2,295 | 257 (246–267) | 53.6 (49.7–57.8) | 13,768 (12,239–15,454) | 3,543 | 396 (383–410) | 5,944 (5,752–6,143) | 19,713 (17,990–21,597) |
| 2013 | 858,557 | 4,379 | 510 (495–525) | 35.2 (33.5–37.0) | 17,962 (16,585–19,450) | 4,994 | 582 (566–598) | 8,725 (8,486–8,970) | 26,687 (25,071–28,421) |
| 2014 | 778,118 | 5,014 | 644 (627–662) | 27.7 (26.5–29.0) | 17,860 (16,591–19,219) | 5,262 | 676 (658–695) | 10,144 (9,873–10,422) | 28,004 (26,465–29,640) |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; PY, person-years.
[a] Confidence intervals around mean prescription costs were calculated using bootstrapping with the percentile method.
[b] The unit cost of a 25-OH-D test was priced at £15.

**Figure 6.3** Time trends in costs arising from vitamin D prescriptions and tests among children in the full study cohort, between 2000 to 2014.[a]




[a] Costs of calciferol prescriptions and 25-OH-D tests are shown separately (red and green lines respectively), as well as combined (blue line). The dashed lines indicate 95% confidence limits.

### *6.4.3.2 Sensitivity Analysis Exploring the Impact of Varying the Unit Cost of 25-OH-D Tests*

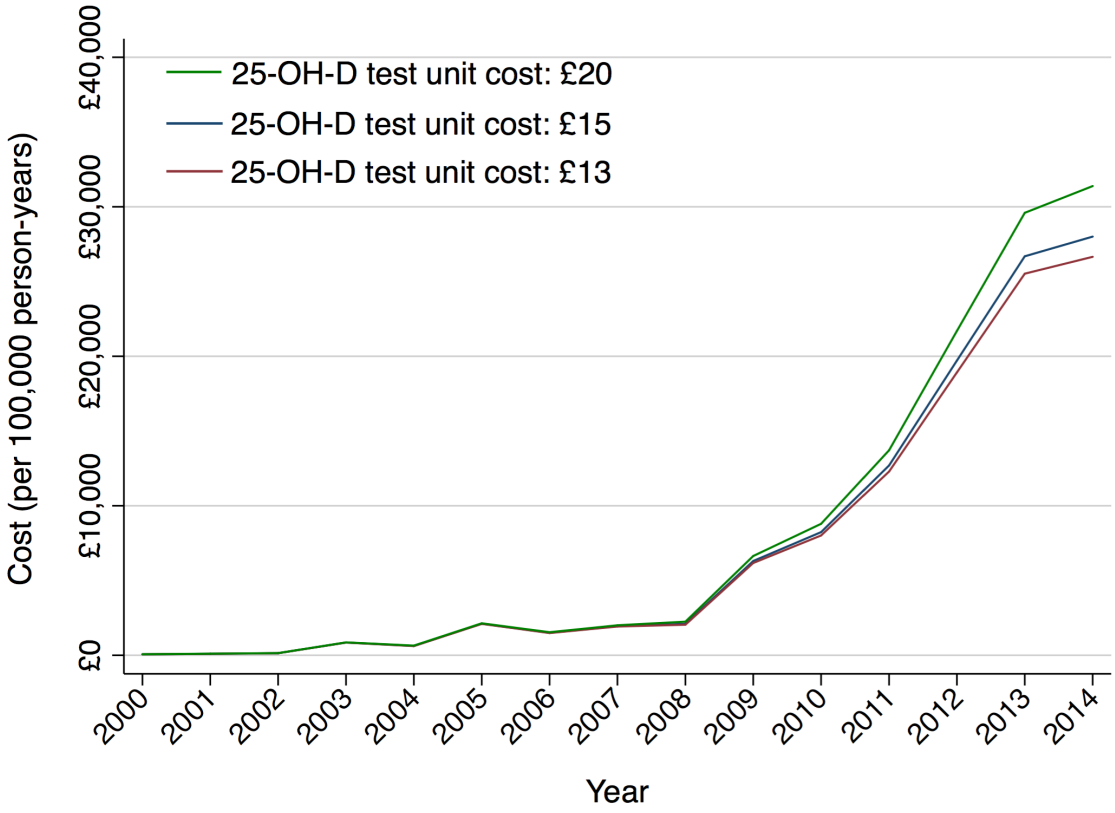
Table 6.9 and Figure 6.4 show the combined costs of vitamin D prescriptions and tests in the full study cohort between 2000 and 2014, using alternative values for the unit cost of a 25-OH-D test. The maximal relative difference in combined costs of vitamin D prescriptions and tests derived using the minimum (£13) and maximum (£20) values for a 25-OH-D test unit cost was 15.1% in 2014.

**Table 6.9** Costs of vitamin D tests, shown separately and combined with the cost of vitamin D prescriptions, in each year between 2000 to 2014, using alternative values for the unit cost of a 25-OH-D test.[a]

| Year | Cost of 25-OH-D tests per 100,000 PY, £ (95% CI) | | | Combined cost of 25-OH-D tests and calciferol prescriptions per 100,000 PY, £ (95% CI) | | |
|---|---|---|---|---|---|---|
| | 25-OH-D test unit cost: £13 | 25-OH-D test unit cost: £15 | 25-OH-D test unit cost: £20 | 25-OH-D test unit cost: £13 | 25-OH-D test unit cost: £15 | 25-OH-D test unit cost: £20 |
| 2000 | 5.94 (1.49–23.8) | 6.86 (1.72–27.4) | 9.14 (2.29–36.6) | 65.1 (28.1–155) | 66.0 (28.3–159) | 68.3 (28.9–168) |
| 2001 | 9.93 (3.73–26.5) | 11.5 (4.30–30.5) | 15.3 (5.73–40.7) | 100 (40.6–242) | 102 (41.2–246) | 105 (42.6–257) |
| 2002 | 10.4 (4.34–25.0) | 12.0 (5.00–28.9) | 16.0 (6.67–38.5) | 139 (43.2–408) | 141 (43.9–412) | 145 (45.6–421) |
| 2003 | 22.3 (12.7–39.3) | 25.8 (14.6–45.3) | 34.3 (19.5–60.5) | 849 (470–1,476) | 852 (472–1,482) | 861 (476–1,497) |
| 2004 | 56.8 (40.6–79.5) | 65.5 (46.8–91.7) | 87.4 (62.4–122) | 616 (322–1,141) | 624 (328–1,153) | 646 (344–1,184) |
| 2005 | 69.9 (52.0–93.9) | 80.7 (60.0–108) | 108 (80.0–145) | 2,100 (1,234–3,479) | 2,111 (1,242–3,494) | 2,138 (1,262–3,530) |
| 2006 | 105 (82.5–133) | 121 (95.2–153) | 161 (127–204) | 1,486 (945–2,365) | 1,502 (958–2,386) | 1,542 (989–2,437) |
| 2007 | 156 (129–189) | 180 (149–218) | 240 (198–291) | 1,921 (1,326–2,792) | 1,945 (1,346–2,821) | 2,005 (1,395–2,894) |
| 2008 | 375 (332–424) | 433 (383–489) | 577 (511–652) | 2,044 (1,508–2,763) | 2,101 (1,559–2,828) | 2,246 (1,687–2,992) |
| 2009 | 870 (803–942) | 1,003 (926–1,087) | 1,338 (1,235–1,449) | 6,173 (4,975–7,716) | 6,306 (5,099–7,860) | 6,641 (5,408–8,223) |
| 2010 | 1,451 (1,364–1,545) | 1,675 (1,573–1,783) | 2,233 (2,098–2,377) | 8,012 (6,837–9,371) | 8,235 (7,047–9,609) | 8,794 (7,571–10,203) |
| 2011 | 2,642 (2,522–2,766) | 3,048 (2,911–3,192) | 4,064 (3,881–4,256) | 12,290 (10,689–14,116) | 12,697 (11,077–14,541) | 13,713 (12,047–15,605) |
| 2012 | 5,152 (4,985–5,324) | 5,944 (5,752–6,143) | 7,926 (7,669–8,191) | 18,920 (17,223–20,778) | 19,713 (17,990–21,597) | 21,694 (19,908–23,645) |
| 2013 | 7,562 (7,355–7,774) | 8,725 (8,486–8,970) | 11,633 (11,315–11,961) | 25,524 (23,940–27,225) | 26,687 (25,071–28,421) | 29,596 (27,900–31,411) |
| 2014 | 8,791 (8,557–9,032) | 10,144 (9,873–10,422) | 13,525 (13,164–13,895) | 26,651 (25,148–28,251) | 28,004 (26,465–29,640) | 31,385 (29,756–33,114) |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; PY, person-years.
[a] The analysis used the full study cohort.

**Figure 6.4** Time trends in healthcare costs arising from vitamin D prescriptions and tests, using alternative unit costs for 25-OH-D tests.[a]




[a] Combined costs of calciferol prescriptions and 25-OH-D tests in the full study cohort between 2000 and 2014 are shown.

### *6.4.3.3 Results Using the Linked THIN-HES Study Cohort*

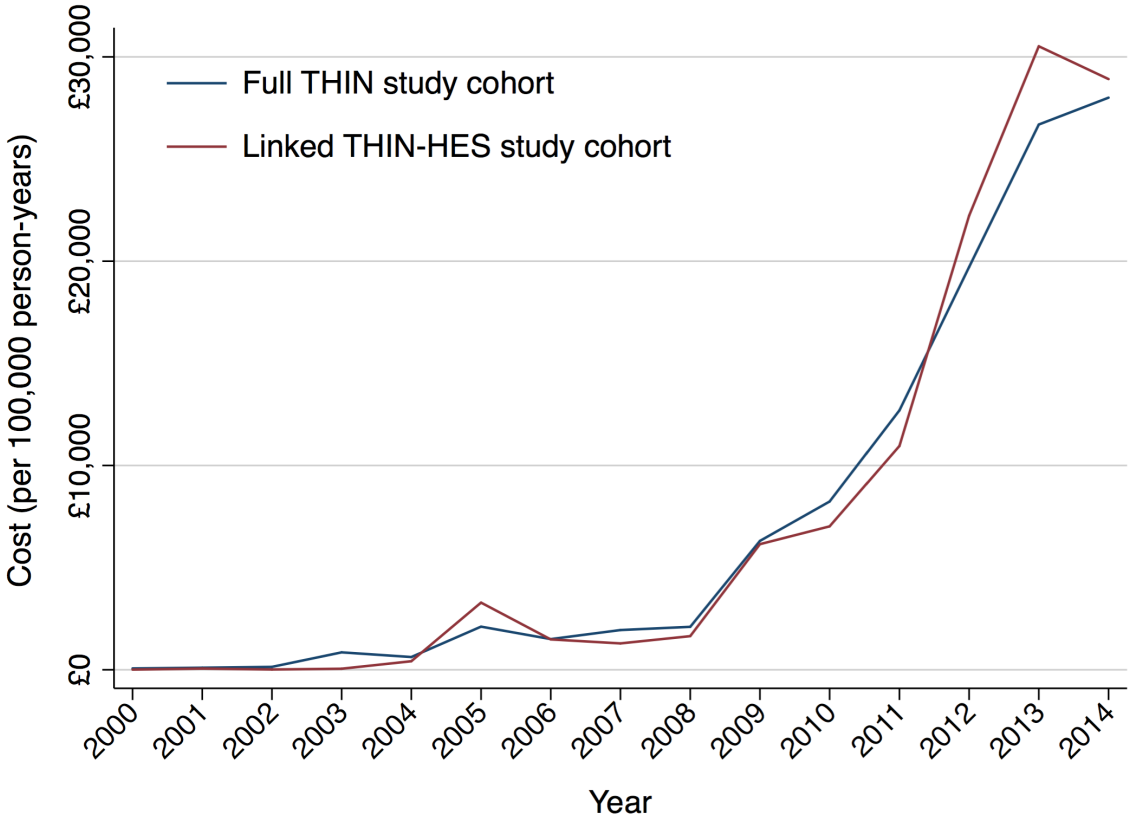
Costs of vitamin D prescriptions and tests in the linked THIN-HES study cohort, between 2000 and 2014, are shown in Table 6.10. Time trends in the combined cost of vitamin D prescriptions and tests observed in the linked THIN-HES study cohort were similar to those seen in the full THIN study cohort (Figure 6.5).

**Table 6.10** Costs of vitamin D prescriptions and tests among children in the linked THIN-HES study cohort, in each year between 2000 to 2014.

| Year | PY of follow-up | Calciferol Prescriptions | | | | 25-OH-D Tests | | | Combined cost of prescriptions & tests per 100,000 PY, £ (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | n | Rate per 100,000 PY (95% CI) | Mean prescription cost, £ (95% CI)[a] | Cost per 100,000 PY, £ (95% CI) | n | Rate per 100,000 PY (95% CI) | Cost per 100,000 PY, £ (95% CI) [b] | |
| 2000 | 161,897 | 0 | 0 | - | - | 1 | 0.62 (0.09–4.38) | 9.27 (1.31–65.8) | 9.27 (1.31–65.8) |
| 2001 | 180,797 | 2 | 1.11 (0.28–4.42) | 37.7 (12.3–63.0) | 41.7 (3.41–279) | 2 | 1.11 (0.28–4.42) | 16.6 (4.15–66.3) | 58.3 (7.56–345) |
| 2002 | 211,593 | 0 | 0 | - | - | 2 | 0.95 (0.24–3.78) | 14.2 (3.55–56.7) | 14.2 (3.55–56.7) |
| 2003 | 222,486 | 1 | 0.45 (0.06–3.19) | 9.10 (9.10–9.10) | 4.09 (0.58–29.0) | 7 | 3.15 (1.50–6.60) | 47.2 (22.5–99.0) | 51.3 (23.1–128) |
| 2004 | 235,500 | 4 | 1.70 (0.64–4.53) | 175 (105–210) | 297 (66.6–950) | 19 | 8.07 (5.15–12.7) | 121 (77.2–190) | 418 (144–1,140) |
| 2005 | 244,548 | 17 | 6.95 (4.32–11.2) | 455 (277–653) | 3,164 (1,197–7,299) | 20 | 8.18 (5.28–12.7) | 123 (79.1–190) | 3,286 (1,276–7,489) |
| 2006 | 251,499 | 18 | 7.16 (4.51–11.4) | 188 (156–210) | 1,349 (703–2,386) | 23 | 9.15 (6.08–13.8) | 137 (91.2–206) | 1,486 (794–2,592) |
| 2007 | 257,336 | 17 | 6.61 (4.11–10.6) | 156 (114–196) | 1,033 (471–2,085) | 44 | 17.1 (12.7–23.0) | 256 (191–345) | 1,290 (662–2,430) |
| 2008 | 265,314 | 22 | 8.29 (5.46–12.6) | 120 (71.8–177) | 997 (392–2,227) | 115 | 43.3 (36.1–52.0) | 650 (542–781) | 1,647 (934–3,007) |
| 2009 | 270,643 | 65 | 24.0 (18.8–30.6) | 201 (136–285) | 4,818 (2,563–8,717) | 240 | 88.7 (78.1–101) | 1,330 (1,172–1,510) | 6,148 (3,735–10,226) |
| 2010 | 278,167 | 106 | 38.1 (31.5–46.1) | 123 (97.4–151) | 4,696 (3,067–6,983) | 431 | 155 (141–170) | 2,324 (2,115–2,554) | 7,020 (5,182–9,537) |
| 2011 | 284,678 | 266 | 93.4 (82.9–105) | 75.9 (59.0–97.7) | 7,092 (4,887–10,298) | 733 | 257 (240–277) | 3,862 (3,593–4,152) | 10,954 (8,480–14,450) |
| 2012 | 288,818 | 913 | 316 (296–337) | 47.6 (42.1–53.5) | 15,034 (12,448–18,015) | 1,385 | 480 (455–505) | 7,193 (6,824–7,582) | 22,227 (19,272–25,597) |
| 2013 | 283,990 | 1,604 | 565 (538–593) | 34.7 (31.7–38.0) | 19,617 (17,032–22,548) | 2,064 | 727 (696–759) | 10,902 (10,441–11,382) | 30,519 (27,473–33,931) |
| 2014 | 253,097 | 1,551 | 613 (583–644) | 28.4 (26.3–30.6) | 17,397 (15,347–19,700) | 1,943 | 768 (734–803) | 11,515 (11,015–12,039) | 28,913 (26,361–31,739) |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; PY, person-years.
[a] Confidence intervals around mean prescription costs were calculated using bootstrapping with the percentile method.
[b] The unit cost of a 25-OH-D test was priced at £15.

**Figure 6.5** Time trends in healthcare costs arising from vitamin D prescriptions and tests, in the full THIN study cohort and in the linked THIN-HES study cohort.[a]




[a] Combined costs of calciferol prescriptions and 25-OH-D tests are shown between 2000 and 2014.

### *6.4.4 National Cost Estimates for Healthcare Expenditure on Vitamin D Testing and Prescribing among Children in Primary Care in England in 2014*

Table 6.11 and 6.12 show the observed costs of vitamin D tests and prescriptions respectively in the linked THIN-HES study cohort in 2014, stratified by age group, sex, and ethnicity. They also show 2014 population estimates for each stratum in England, and estimated total costs of vitamin D tests and prescriptions nationally in each population stratum. The total cost of vitamin D prescriptions and tests for children in primary care in England in 2014 was estimated to be £4.29 million (95% CI: 2.94 to 6.44), of which the cost of calciferol prescriptions was £2.60 million (95% CI: 1.64 to 4.20) and the cost of 25-OH-D tests was £1.69 million (95% CI: 1.31 to 2.24).

**Table 6.11** Stratified costs of vitamin D tests in the linked THIN-HES study cohort and national estimates for England in 2014.

| Stratum | | | Stratified rates and costs of 25-OH-D tests in the study cohort in 2014 [a] | | | | National estimates for England in 2014 | |
|---|---|---|---|---|---|---|---|---|
| **Ethnicity** | **Age group** | **Sex** | **PY of follow-up** | **No. of 25-OH-D tests** | **Rate per 100,000 PY (95% CI)** | **Cost per 100,000 PY, £ (95% CI) [b]** | **Population estimate** | **Cost of 25-OH-D tests, £ (95% CI)** |
| White | 0-4 years | *Male* | 27,535 | 49 | 178 (134–235) | 2,669 (2,017–3,532) | 1,337,468 | 35,701 (26,983–47,237) |
| | | *Female* | 26,289 | 42 | 160 (118–216) | 2,396 (1,771–3,243) | 1,268,515 | 30,399 (22,465–41,134) |
| | 5-9 years | *Male* | 29,154 | 69 | 237 (187–300) | 3,550 (2,804–4,495) | 1,298,411 | 46,096 (36,407–58,362) |
| | | *Female* | 27,975 | 77 | 275 (220–344) | 4,129 (3,302–5,162) | 1,233,489 | 50,927 (40,733–63,672) |
| | 10-14 years | *Male* | 25,984 | 99 | 381 (313–464) | 5,715 (4,693–6,959) | 1,224,417 | 69,976 (57,465–85,212) |
| | | *Female* | 24,244 | 111 | 458 (380–551) | 6,868 (5,702–8,272) | 1,166,551 | 80,115 (66,515–96,495) |
| | 15-17 years | *Male* | 15,878 | 70 | 441 (349–557) | 6,613 (5,232–8,359) | 802,058 | 53,041 (41,964–67,042) |
| | | *Female* | 15,177 | 224 | 1,476 (1,295–1,682) | 22,139 (19,421–25,236) | 762,486 | 168,806 (148,086–192,424) |
| Asian | 0-4 years | *Male* | 2,271 | 48 | 2,113 (1,593–2,804) | 31,701 (23,890–42,066) | 179,903 | 57,030 (42,978–75,677) |
| | | *Female* | 2,299 | 37 | 1,609 (1,166–2,221) | 24,139 (17,489–33,316) | 172,680 | 41,683 (30,201–57,530) |
| | 5-9 years | *Male* | 2,343 | 87 | 3,713 (3,009–4,581) | 55,690 (45,136–68,713) | 171,776 | 95,663 (77,533–118,032) |
| | | *Female* | 2,180 | 97 | 4,449 (3,646–5,428) | 66,733 (54,690–81,426) | 164,570 | 109,822 (90,004–134,003) |
| | 10-14 years | *Male* | 1,672 | 82 | 4,905 (3,951–6,091) | 73,580 (59,260–91,361) | 134,858 | 99,229 (79,917–123,208) |
| | | *Female* | 1,709 | 121 | 7,080 (5,924–8,461) | 106,196 (88,864–126,908) | 127,544 | 135,447 (113,341–161,864) |
| | 15-17 years | *Male* | 843 | 46 | 5,460 (4,089–7,289) | 81,893 (61,340–109,332) | 80,239 | 65,710 (49,218–87,727) |
| | | *Female* | 834 | 117 | 14,029 (11,704–16,816) | 210,433 (175,558–252,237) | 74,448 | 156,663 (130,699–187,785) |
| Black | 0-4 years | *Male* | 1,198 | 11 | 918 (508–1,658) | 13,771 (7,626–24,866) | 91,967 | 12,664 (7,014–22,868) |
| | | *Female* | 1,150 | 17 | 1,478 (919–2,378) | 22,176 (13,786–35,672) | 89,322 | 19,808 (12,314–31,863) |
| | 5-9 years | *Male* | 1,382 | 31 | 2,243 (1,578–3,190) | 33,652 (23,666–47,850) | 86,319 | 29,048 (20,428–41,304) |
| | | *Female* | 1,401 | 30 | 2,141 (1,497–3,062) | 32,116 (22,455–45,933) | 84,422 | 27,113 (18,957–38,778) |
| | 10-14 years | *Male* | 1,125 | 26 | 2,311 (1,574–3,394) | 34,667 (23,604–50,916) | 70,192 | 24,334 (16,568–35,739) |
| | | *Female* | 1,099 | 58 | 5,279 (4,081–6,829) | 79,187 (61,219–102,428) | 69,190 | 54,789 (42,357–70,870) |

**Table 6.11** continued.

| Stratum | | | Stratified rates and costs of 25-OH-D tests in the study cohort in 2014 [a] | | | | National estimates for England in 2014 | |
|---|---|---|---|---|---|---|---|---|
| **Ethnicity** | **Age group** | **Sex** | **PY of follow-up** | **No. of 25-OH-D tests** | **Rate per 100,000 PY (95% CI)** | **Cost per 100,000 PY, £ (95% CI) [b]** | **Population estimate** | **Cost of 25-OH-D tests, £ (95% CI)** |
| Black | 15-17 years | *Male* | 688 | 13 | 1,891 (1,098–3,256) | 28,361 (16,468–48,843) | 42,733 | 12,120 (7,037–20,872) |
| | | *Female* | 718 | 54 | 7,518 (5,758–9,816) | 112,766 (86,367–147,236) | 42,508 | 47,935 (36,713–62,587) |
| Mixed | 0-4 years | *Male* | 1,083 | 4 | 369 (139–984) | 5,540 (2,079–14,761) | 113,209 | 6,272 (2,354–16,711) |
| | | *Female* | 1,045 | 6 | 574 (258–1,278) | 8,613 (3,869–19,171) | 109,334 | 9,417 (4,231–20,961) |
| | 5-9 years | *Male* | 1,153 | 10 | 867 (467–1,612) | 13,007 (6,998–24,174) | 89,212 | 11,604 (6,243–21,566) |
| | | *Female* | 1,163 | 6 | 516 (232–1,149) | 7,740 (3,477–17,229) | 86,002 | 6,657 (2,991–14,817) |
| | 10-14 years | *Male* | 683 | 12 | 1,758 (998–3,096) | 26,371 (14,976–46,435) | 67,736 | 17,862 (10,144–31,453) |
| | | *Female* | 666 | 21 | 3,151 (2,055–4,833) | 47,272 (30,821–72,502) | 65,479 | 30,953 (20,182–47,473) |
| | 15-17 years | *Male* | 318 | 6 | 1,887 (848–4,201) | 28,310 (12,718–63,014) | 38,506 | 10,901 (4,897–24,264) |
| | | *Female* | 272 | 8 | 2,938 (1,469–5,875) | 44,075 (22,042–88,132) | 37,094 | 16,349 (8,176–32,692) |
| Other | 0-4 years | *Male* | 654 | 6 | 918 (412–2,043) | 13,766 (6,184–30,641) | 35,194 | 4,845 (2,177–10,784) |
| | | *Female* | 635 | 2 | 315 (79–1,259) | 4,724 (1,182–18,890) | 33,366 | 1,576 (394–6,303) |
| | 5-9 years | *Male* | 561 | 8 | 1,427 (713–2,852) | 21,398 (10,701–42,787) | 29,430 | 6,297 (3,149–12,592) |
| | | *Female* | 589 | 6 | 1,018 (457–2,266) | 15,268 (6,860–33,986) | 28,733 | 4,387 (1,971–9,765) |
| | 10-14 years | *Male* | 579 | 11 | 1,899 (1,052–3,429) | 28,488 (15,777–51,442) | 24,294 | 6,921 (3,833–12,497) |
| | | *Female* | 541 | 26 | 4,802 (3,270–7,053) | 72,034 (49,046–105,797) | 22,794 | 16,419 (11,179–24,115) |
| | 15-17 years | *Male* | 441 | 7 | 1,587 (757–3,330) | 23,810 (11,351–49,943) | 18,551 | 4,417 (2,106–9,265) |
| | | *Female* | 379 | 18 | 4,750 (2,993–7,540) | 71,253 (44,893–113,093) | 16,702 | 11,901 (7,498–18,889) |
| **TOTAL** | | | 225,910 | 1,773 | - | - | 11,591,701 | 1,690,895 (1,307,422–2,236,434) |

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; PY, person-years.
[a] Missing data for ethnicity was handled using complete cases analysis. N = 268,221.
[b] The unit cost of a 25-OH-D test was priced at £15.

**Table 6.12** Stratified costs of vitamin D prescriptions in the linked THIN-HES study cohort and national estimates for England in 2014.

| Stratum | | | Stratified rates and costs of calciferol prescriptions in the study cohort in 2014 [a] | | | | | National estimates for England in 2014 | |
|---|---|---|---|---|---|---|---|---|---|
| Ethnicity | Age, years | Sex | PY of follow-up | No. of prescriptions | Rate per 100,000 PY (95% CI) | Mean unit cost, £ (95% CI) [b] | Cost per 100,000 PY, £ (95% CI) | Population estimate | Cost of calciferol prescriptions, £ (95% CI) |
| White | 0–4 | *Male* | 27,535 | 29 | 105 (73–152) | 57.3 (48.3–66.3) | 6,037 (3,537–10,050) | 1,337,468 | 80,743 (47,307–134,420) |
| | | *Female* | 26,289 | 11 | 42 (23–76) | 57.3 (48.3–66.3) | 2,398 (1,120–5,010) | 1,268,515 | 30,424 (14,205–63,556) |
| | 5–9 | *Male* | 29,154 | 78 | 268 (214–334) | 47.9 (41.8–54.0) | 12,818 (8,967–18,030) | 1,298,411 | 166,435 (116,430–234,101) |
| | | *Female* | 27,975 | 31 | 111 (78–158) | 47.9 (41.8–54.0) | 5,309 (3,261–8,505) | 1,233,489 | 65,487 (40,223–104,910) |
| | 10–14 | *Male* | 25,984 | 114 | 439 (365–527) | 22.6 (19.4–25.8) | 9,904 (7,073–13,588) | 1,224,417 | 121,265 (86,608–166,372) |
| | | *Female* | 24,244 | 87 | 359 (291–443) | 22.6 (19.4–25.8) | 8,101 (5,634–11,413) | 1,166,551 | 94,498 (65,722–133,139) |
| | 15–17 | *Male* | 15,878 | 60 | 378 (293–487) | 16.3 (13.9–18.6) | 6,142 (4,092–9,033) | 802,058 | 49,262 (32,821–72,450) |
| | | *Female* | 15,177 | 148 | 975 (830–1,146) | 16.3 (13.9–18.6) | 15,850 (11,576–21,263) | 762,486 | 120,851 (88,269–162,126) |
| Asian | 0–4 | *Male* | 2,271 | 25 | 1,101 (744–1,629) | 57.3 (48.3–66.3) | 63,094 (35,944–108,023) | 179,903 | 113,507 (64,664–194,337) |
| | | *Female* | 2,299 | 19 | 826 (527–1,296) | 57.3 (48.3–66.3) | 47,368 (25,473–85,912) | 172,680 | 81,795 (43,987–148,353) |
| | 5–9 | *Male* | 2,343 | 55 | 2,347 (1,802–3,057) | 47.9 (41.8–54.0) | 112,450 (75,402–165,012) | 171,776 | 193,163 (129,523–283,452) |
| | | *Female* | 2,180 | 42 | 1,926 (1,424–2,607) | 47.9 (41.8–54.0) | 92,290 (59,568–140,694) | 164,570 | 151,881 (98,031–231,540) |
| | 10–14 | *Male* | 1,672 | 74 | 4,427 (3,525–5,560) | 22.6 (19.4–25.8) | 99,929 (68,279–143,307) | 134,858 | 134,763 (92,080–193,262) |
| | | *Female* | 1,709 | 129 | 7,548 (6,352–8,969) | 22.6 (19.4–25.8) | 170,383 (123,034–231,203) | 127,544 | 217,313 (156,923–294,886) |
| | 15–17 | *Male* | 843 | 45 | 5,341 (3,988–7,153) | 16.3 (13.9–18.6) | 86,806 (55,614–132,762) | 80,239 | 69,652 (44,624–106,527) |
| | | *Female* | 834 | 130 | 15,588 (13,126–18,511) | 16.3 (13.9–18.6) | 253,350 (183,059–343,567) | 74,448 | 188,613 (136,284–255,778) |
| Black | 0–4 | *Male* | 1,198 | 17 | 1,419 (882–2,282) | 57.3 (48.3–66.3) | 81,326 (42,625–151,346) | 91,967 | 74,793 (39,201–139,188) |
| | | *Female* | 1,150 | 7 | 609 (290–1,277) | 57.3 (48.3–66.3) | 34,894 (14,025–84,678) | 89,322 | 31,168 (12,528–75,636) |
| | 5–9 | *Male* | 1,382 | 21 | 1,520 (991–2,331) | 47.9 (41.8–54.0) | 72,812 (41,462–125,814) | 86,319 | 62,850 (35,790–108,601) |
| | | *Female* | 1,401 | 23 | 1,641 (1,091–2,470) | 47.9 (41.8–54.0) | 78,643 (45,643–133,330) | 84,422 | 66,393 (38,533–112,561) |
| | 10–14 | *Male* | 1,125 | 36 | 3,200 (2,308–4,436) | 22.6 (19.4–25.8) | 72,238 (44,714–114,355) | 70,192 | 50,705 (31,385–80,268) |
| | | *Female* | 1,099 | 65 | 5,916 (4,639–7,544) | 22.6 (19.4–25.8) | 133,552 (89,870–194,470) | 69,190 | 92,405 (62,181–134,554) |

**Table 6.12** continued.

| Stratum | | | Stratified rates and costs of calciferol prescriptions in the study cohort in 2014 [a] | | | | | National estimates for England in 2014 | |
|---|---|---|---|---|---|---|---|---|---|
| **Ethnicity** | **Age, years** | **Sex** | **PY of follow-up** | **No. of prescriptions** | **Rate per 100,000 PY (95% CI)** | **Mean unit cost, £ (95% CI) [b]** | **Cost per 100,000 PY, £ (95% CI)** | **Population estimate** | **Cost of calciferol prescriptions, £ (95% CI)** |
| Black | 15–17 | *Male* | 688 | 13 | 1,891 (1,098–3,256) | 16.3 (13.9–18.6) | 30,731 (15,311–60,435) | 42,733 | 13,132 (6,543–25,826) |
| | | *Female* | 718 | 52 | 7,239 (5,516–9,500) | 16.3 (13.9–18.6) | 117,662 (76,935–176,325) | 42,508 | 50,016 (32,704–74,953) |
| Mixed | 0–4 | *Male* | 1,083 | 3 | 277 (89–859) | 57.3 (48.3–66.3) | 15,878 (4,318–56,955) | 113,209 | 17,975 (4,888–64,478) |
| | | *Female* | 1,045 | 7 | 670 (319–1,405) | 57.3 (48.3–66.3) | 38,398 (15,434–93,182) | 109,334 | 41,983 (16,874–101,879) |
| | 5–9 | *Male* | 1,153 | 10 | 867 (467–1,612) | 47.9 (41.8–54.0) | 41,544 (19,523–86,989) | 89,212 | 37,062 (17,417–77,605) |
| | | *Female* | 1,163 | 1 | 86 (12–611) | 47.9 (41.8–54.0) | 4,120 (507–32,955) | 86,002 | 3,544 (436–28,341) |
| | 10–14 | *Male* | 683 | 8 | 1,172 (586–2,344) | 22.6 (19.4–25.8) | 26,457 (11,354–60,410) | 67,736 | 17,921 (7,691–40,919) |
| | | *Female* | 666 | 15 | 2,251 (1,357–3,734) | 22.6 (19.4–25.8) | 50,814 (26,288–96,247) | 65,479 | 33,273 (17,213–63,022) |
| | 15–17 | *Male* | 318 | 9 | 2,831 (1,473–5,441) | 16.3 (13.9–18.6) | 46,012 (20,543–100,982) | 38,506 | 17,717 (7,910–38,884) |
| | | *Female* | 272 | 5 | 1,836 (764–4,412) | 16.3 (13.9–18.6) | 29,848 (10,660–81,888) | 37,094 | 11,072 (3,954–30,376) |
| Other | 0–4 | *Male* | 654 | 1 | 153 (22–1,086) | 57.3 (48.3–66.3) | 8,767 (1,041–72,005) | 35,194 | 3,086 (366–25,341) |
| | | *Female* | 635 | 2 | 315 (79–1,259) | 57.3 (48.3–66.3) | 18,053 (3,807–83,511) | 33,366 | 6,024 (1,270–27,864) |
| | 5–9 | *Male* | 561 | 7 | 1,248 (595–2,618) | 47.9 (41.8–54.0) | 59,802 (24,899–141,324) | 29,430 | 17,600 (7,328–41,592) |
| | | *Female* | 589 | 12 | 2,036 (1,156–3,585) | 47.9 (41.8–54.0) | 97,535 (48,377–193,492) | 28,733 | 28,025 (13,900–55,596) |
| | 10–14 | *Male* | 579 | 9 | 1,554 (809–2,986) | 22.6 (19.4–25.8) | 35,078 (15,662–76,982) | 24,294 | 8,522 (3,805–18,702) |
| | | *Female* | 541 | 21 | 3,879 (2,529–5,949) | 22.6 (19.4–25.8) | 87,559 (48,989–153,345) | 22,794 | 19,958 (11,166–34,953) |
| | 15–17 | *Male* | 441 | 3 | 680 (219–2,109) | 16.3 (13.9–18.6) | 11,057 (3,060–39,147) | 18,551 | 2,051 (568–7,262) |
| | | *Female* | 379 | 12 | 3,167 (1,798–5,576) | 16.3 (13.9–18.6) | 51,471 (25,082–103,495) | 16,702 | 8,597 (4,189–17,286) |
| **TOTAL** | | | 225,910 | 1,436 | - | - | - | 11,591,701 | 2,595,523 (1,635,542–4,204,896) |

Abbreviations: CI, confidence interval; PY, person-years.
[a] Missing data for ethnicity was handled using complete cases analysis. N = 268,221.
[b] The mean unit costs for calciferol prescriptions in each age group category, see Table 6.4.

## 6.5 Discussion

### *6.5.1 Summary of Results and Comparison with Existing Studies*

Among children in the UK, a marked increase in healthcare expenditure on vitamin D tests and prescriptions in primary care was observed between 2008 and 2014. The magnitude of the increase was approximately 13-fold. This mirrors trends in the diagnosis of vitamin D deficiency in children in clinical practice over the same time-period, described in chapter 5. Applying the observed rates of expenditure in the study cohort to national population estimates, the overall cost of vitamin D testing and prescribing for children in primary care in England in 2014 was estimated to be £4.29 million (95% CI: 2.94 to 6.44).

This is the first study to report estimates for healthcare expenditure related to vitamin D testing and treatment specifically among children. However previous publications, described below, have reported time trends in healthcare costs arising from vitamin D tests and prescriptions among general populations, including adults as well as children. These have generally reported a similar pattern to the results described in this chapter, with large increases in expenditure observed over the last decade. Overall NHS expenditure on vitamin D prescriptions dispensed by community pharmacies in England, reported in Prescription Cost Analysis data, increased from £28 million in 2004 to £92 million in 2014 (HSCIC, 2005; 2015b). National healthcare expenditure on 25-OH-D tests in Australia is reported to have increased from $1 million Australian dollars in 2000 to $95.6 million Australian dollars in 2010 (Bilinski & Boyages, 2012), whilst expenditure on vitamin D tests in the Ontario province of Canada increased from $38 million Canadian dollars in 2009 to a projected $150 million Canadian dollars in 2012 (Bilinski & Boyages, 2012).

Variation in the average cost of calciferol prescriptions for children was observed over the study period. Between 2003 to 2010 the mean prescription cost was greater than £100, and then decreased between 2011 and 2014 to £27.72. This may reflect efforts by local commissioning groups and pharmacy services in more recent years to encourage the prescription of less costly vitamin D products (Rehman & Rai, 2012). However, it should be noted that the unit costs for different calciferol preparations were kept constant at 2014 prices in the analyses, and therefore changes in the price of different preparations over time were not taken into account. This approach was taken

to ensure that that analysis of time-trends in expenditure represented changes in levels of healthcare activity over time rather than changes in the monetary value of drugs.

### *6.5.2 Study Strengths*

THIN is a prospectively collected database of electronic healthcare records from UK primary care. As it contains routine consultation data, it is representative of real life, contemporary clinical practice. The longitudinal nature of the data allowed investigation of trends in the healthcare expenditure over time. The large sample size of the THIN database allowed stratification of rates of expenditure on vitamin D tests and prescriptions by several demographic factors (age group, sex, and ethnicity).

The vast majority of the UK population is registered with a general practice, and the THIN cohort has been shown to be broadly representative of the UK population as a whole in terms of age and sex distribution, mortality rates, and the prevalence of various chronic medical conditions (Blak et al, 2011). Furthermore, the recording of consultations and prescriptions in THIN practices is comparable to national primary care statistics (Bourke et al, 2004). Therefore, the results of the study should be broadly generalisable to children in the UK as a whole.

Medication prescriptions in primary care are particularly well recorded in THIN, as they are issued electronically by general practitioners (GPs) and automatically captured in the electronic patient record (Thiru et al, 2003). Laboratory test results are also well recorded, as the majority of THIN practices are electronically linked to pathology laboratories, with the results of tests requested in primary care sent electronically to practices and automatically stored in patients' electronic health records (CSDMRUK, 2010). Therefore, healthcare resource use regarding vitamin D prescription and testing in primary care is likely to have been accurately captured using the THIN data source.

### *6.5.3 Study Limitations*

A key limitation of the study is that only healthcare costs are examined, without investigation of health benefits resulting from vitamin D testing and prescribing in children. Thus, the work represents a cost of illness study as opposed to a full health economic evaluation, and does not on its own provide information regarding whether or not the expenditure is an efficient use of healthcare resources (Byford et al, 2000). It

was not possible to estimate potential health benefits of treatment from the data available in the THIN database, as reliable information was not available regarding the clinical condition, or indications for testing and treatment, among cases (see chapter 5.4.6). There are no previous studies that have investigated the clinical presentation of children diagnosed with vitamin D deficiency in primary care, and therefore this information was not available from existing work.

A further important limitation of the study is that the results represent a proportion of, rather than total, direct healthcare costs for the NHS associated with vitamin D deficiency diagnosis and treatment in children. The study is limited to healthcare resource use in primary care, as the costs of vitamin D prescribing and testing in secondary care were not captured. Furthermore, reliable resource use data was not available regarding healthcare consultations arising as a direct consequence of the investigation or management of vitamin D deficiency. Although data regarding GP consultations and referrals to secondary care are recorded in THIN, information regarding the principal clinical reason for consultation episodes is not specifically coded. Therefore, it was not possible to reliably determine whether consultation episodes in patients' medical records were primarily related to the investigation or management of vitamin D deficiency, or had arisen as a result of other clinical symptoms or comorbidities with vitamin D deficiency a secondary issue.

There was a substantial degree of uncertainty, with relatively wide 95% confidence intervals, around the derived national cost estimates for children in England in 2014. This was particularly the case for the estimated cost of calciferol prescriptions. Factors contributing to this uncertainty included the small numbers of outcome events in some of the population strata, and the uncertainty around the mean calciferol prescription cost estimates.

Other relevant limitations of THIN and HES data, including the under-representation of individuals from the most deprived areas of the country in THIN, and issues concerning the accuracy of ethnicity recording, have been discussed in chapter 5.5.3.

### *6.5.4 Conclusion*

In summary, the results described in this chapter demonstrate that there has been a marked increase in healthcare expenditure on vitamin D tests and prescriptions for children in primary care in the UK between 2008 and 2014. The results do not

represent total NHS healthcare expenditure associated with the diagnosis and management of vitamin D deficiency among children. However, they do give some insight into the economic consequence of the increase in diagnosis of vitamin D deficiency among children in clinical practice over the last decade, described in chapter 5. The implications of the work described in this chapter, with respect to health services, clinical practice and future research, are discussed in the final chapter of the thesis.

# Chapter 7

# Discussion

## 7.1 Introduction

Vitamin D has attracted considerable clinical and academic interest over the last two decades. In relation to child health, there are concerns that clinical complications of vitamin D deficiency have increased in frequency among children in developed countries such as the UK, USA, and Australia (Ahmed et al, 2011; Allgrove, 2004; Holick, 2006; Robinson et al, 2006; Shaw & Pal, 2002). In the UK, this has generated criticism of national public health policy regarding the prevention of vitamin D deficiency (Davies & Shaw, 2011; Högler, 2015; Hyppönen & Boucher, 2010), and prompted the Department of Health to commission a review of the Healthy Start vitamin programme (Lemer, 2013; NICE, 2015). However, these concerns have largely been based upon anecdotal reports and local case series, and quantitative evaluation of the epidemiology of symptomatic vitamin D deficiency has been limited.

There has also been considerable debate and controversy regarding the possibility that vitamin D may have clinically relevant physiological activity beyond its established role in calcium and bone metabolism, and that vitamin D deficiency *may* increase the risk of various non-musculoskeletal diseases (SACN, 2016; Theodoratou et al, 2014). As vitamin D has attracted increasing attention, large increases in vitamin D testing and prescribing have been reported in adult practice over the last decade, with significant associated healthcare costs (Bilinski & Boyages, 2012; 2013; HSCIC, 2005; 2015b). However, the influence of the increased interest in vitamin D on paediatric clinical practice has not been explored.

The overall aims of the studies described in this thesis were to examine the epidemiology of symptomatic vitamin D deficiency in children, explore temporal trends in the diagnosis of vitamin D deficiency in clinical practice, and investigate healthcare expenditure related to vitamin D testing and prescribing in children. In this chapter, the main results from the work described in the thesis are summarised. The implications of the research findings for public health policy, health services and clinical practice are discussed, and recommendations for future research are made.

## 7.2 Summary of the Thesis and its Main Findings

### *7.2.1 Epidemiology of Symptomatic Vitamin D Deficiency in Children*

Chapter 3 set out to systematically review the published literature regarding the incidence of symptomatic vitamin D deficiency among children worldwide, between 1990 and 2016. Thirteen unique studies were identified, the majority of which originated from Europe and North America. There was considerable heterogeneity among the included studies with respect to their study populations, clinical outcomes, and methodological characteristics. There was also a large variation in the quality of included studies, and their assessed risk of bias.

When considering the subset of higher-quality studies considered to have a lower risk of bias, it was possible to gain some insight into the epidemiology of symptomatic vitamin D deficiency among children from high-income countries with populations of predominantly Caucasian ethnicity. Data is lacking from other regions of the world, including Africa, Asia, the Middle East, and South America. Among studies that included both children presenting with musculoskeletal features of rickets and children with sequelae of hypocalcaemia, annual incidence estimates ranged between 2.2 to 7.5 per 100,000 children. A pooled summary estimate for the annual incidence of symptomatic vitamin D deficiency, derived from four of the higher quality studies, was 3.37 per 100,000 children aged from birth to adolescence (95% CI: 2.15 to 4.60). The pooled incidence estimate should be interpreted with caution, given the high level of statistical heterogeneity observed ($I^2$ = 88%).

Although few studies examined differences in the incidence of symptomatic vitamin D deficiency in relation to children's demographic characteristics, the limited data available suggests that its incidence is considerably higher among young children aged ≤2 years compared to older children, and among children from South Asian, black and Middle Eastern ethnic minority groups compared to white children. Although anecdotal reports and local case series have raised concerns that symptomatic vitamin D deficiency may have increased in frequency among children in high-income countries in recent decades, there is insufficient epidemiological data available to draw any conclusions regarding temporal trends in incidence over the last 25 years.

Although the systematic review involved a comprehensive search of the published literature, using multiple bibliographic databases, unpublished literature was not

specifically sought, and study assessment was undertaken by a single researcher as opposed to independent double screening as recommended by published guidelines (Liberati et al, 2009). In view of the limited number of included studies, it was not possible to perform subgroup analysis to investigate sources of heterogeneity, or meta-regression to examine differences in incidence rates in relation to demographic factors.

The systematic review identified that the few existing studies investigating symptomatic vitamin D deficiency among UK children were regional studies, with limited generalisability to the national population. The prospective surveillance study described in chapter 4 set out to determine the incidence of one of the most common acute presentations of vitamin D deficiency, hypocalcaemic seizures, nationally among children across the UK and Ireland using the British Paediatric Surveillance Unit reporting system. There were 92 confirmed or probable cases reported over a 2-year study period between September 2011 to September 2013, equating to an overall annual incidence of 3.53 per million children aged 0 to 15 years (95% CI: 2.84 to 4.33).

Hypocalcaemic seizures secondary to vitamin D deficiency were observed in two distinct age groups; young children aged between 0 to 2 years, and adolescents. The highest incidence was among infants aged <1 year. Incidence was 4-fold higher among males compared to females, and was considerably higher among children from South Asian and black ethnic groups compared to those from white ethnic backgrounds. Overall, clinical outcomes were good, with no deaths reported and one child reported to have sequelae at the time of discharge (an extravasation injury from intravenous calcium gluconate). In a minority of cases (13%), it was reported that children did not receive vitamin D replacement in the form of treatment doses of colecalciferol or ergocalciferol, as recommended by national and international guidelines, and instead received only multivitamin supplements or activated analogues of vitamin D.

This is the first study in the UK to report national incidence estimates for any of the clinical manifestations of vitamin D deficiency. However, it is limited to one of the acute presentations of vitamin D deficiency, and does not represent the overall health burden caused by vitamin D deficiency in childhood. The main strength of the study was the use of an established active surveillance system, with national coverage, and consistently high response rates. However, a degree of under-ascertainment of cases is likely with any voluntary surveillance system, and there was no additional secondary source of case ascertainment available for the study outcome. Furthermore, it was not possible to confirm case status for a minority (7%) of reported cases. In some cases

pathology other than vitamin D deficiency may have contributed to the development of hypocalcaemia, such as immaturity of the parathyroid axis in neonates.

### 7.2.2 Trends in the Diagnosis of Vitamin D Deficiency in Children, and Associated Cost Implications

The cohort study described in chapter 5 set out to determine temporal trends in the diagnosis of vitamin D Deficiency in children in clinical practice, and explore differences in diagnosis by children's socio-demographic characteristics. The study utilised prospectively collected electronic healthcare records from UK primary care, held in the Health Improvement Network (THIN) database. Linked Hospital Episode Statistics (HES) data, available for a subset of the cohort, was used to maximise the availability of data regarding ethnicity. Missing data for ethnicity was further minimised by linkage of children to mothers, and use of maternal ethnicity as a proxy measure for children whose ethnicity was not recorded.

A marked increase in the diagnosis of vitamin D deficiency in clinical practice was observed among children in the UK over the past decade. Between 2000 and 2008, overall rates of diagnosis of vitamin D deficiency were below 10 per 100,000 person-years. Between 2008 and 2013 this increased to over 200 per 100,000 person-years, after which rates plateaued between 2013 to 2014. After accounting for temporal changes in socio-demographic characteristics of the cohort, an increase in diagnosis of approximately 15-fold (95% CI: 10 to 21) was seen between 2008 to 2014.

Vitamin D deficiency was diagnosed considerably more frequently in children from South Asian and black ethnic minority groups compared to those from white ethnic backgrounds. Diagnosis was more common in older compared to younger children, and among children from more deprived backgrounds. Among older children aged ≥10 years, rates of diagnosis were higher in girls compared to boys.

The THIN dataset is large and representative of real life clinical practice. The THIN cohort has been shown to be broadly representative of the UK population as a whole in terms of age and sex distribution, mortality rates, prevalence of chronic medical conditions, and primary care consultation and prescription rates. (Blak et al, 2011; Bourke et al, 2004). Therefore, the results of the study should be broadly generalisable to children in the UK as a whole. However, THIN has been shown to be somewhat

under-representative of individuals from the most deprived areas. Although vitamin D prescriptions and tests were included in the case definition to minimise case under-ascertainment, it is possible that some cases may still have been missed. For example, children who were diagnosed and received their full course of treatment in secondary care would have been missed if the diagnosis was not subsequently entered into the primary care record from hospital correspondence. A key limitation of the data was poor recording of information regarding the clinical presentation of cases, which prevented meaningful exploration of the clinical indications prompting investigation of vitamin D status in children.

The cohort study described in chapter 6 set out to the explore the economic implications of the change in diagnostic behaviour identified in chapter 5. Using the THIN database, the study examined longitudinal trends in healthcare expenditure arising from vitamin D testing and prescribing among children in primary care, and demonstrated a marked increase in expenditure of approximately 13-fold between 2008 (£2,101 per 100,000 person-years,) and 2014 (£28,004 per 100,000 person-years). Applying the observed rates of expenditure in the study cohort to national population estimates, the overall cost of vitamin D testing and prescribing for children in primary care in England in 2014 was estimated to be £4.29 million (95% CI: 2.94 to 6.44). The observed increase in expenditure mirrors trends in healthcare spending on vitamin D tests and prescriptions reported in adult practice in England, Australia, and Canada over the last decade (Bilinski & Boyages, 2012; 2013; HSCIC, 2005; 2015b).

Data regarding prescriptions issued in primary care and laboratory test results are particularly well recorded in THIN, as a result of computerised prescribing and electronic linkage with laboratory services. However, the study was limited to healthcare resource use in primary care, and did not capture the costs of vitamin D testing and prescribing in secondary care. Furthermore, reliable resource use data was not available for GP consultations, referrals to secondary care or hospital admissions, as it was not known whether episodes in patient's medical records were primarily related to the investigation or management of vitamin D deficiency, or had arisen as a result of other clinical symptoms or comorbidities with vitamin D deficiency a secondary issue. Therefore, the results do not represent total National Health Service (NHS) healthcare expenditure associated with the diagnosis and management of vitamin D deficiency among children, although they do indicate a clear trend for increasing costs over the last decade.

## 7.3 Implications for Public Health

The results from the systematic review and the BPSU surveillance study demonstrate that, whilst uncommon, symptomatic complications of vitamin D deficiency are occurring among children in the UK and in other high income countries with predominantly Caucasian populations. In these settings, children from high-risk ethnic minority groups, namely those from South Asian, black, and Middle Eastern backgrounds, are disproportionately affected. However, severe complications of vitamin D deficiency are not limited to children from high-risk ethnic groups and, although rare, also occur in children from white backgrounds.

Although uncommon, symptomatic vitamin D deficiency can cause considerable morbidity amongst affected children. Almost all of the children with hypocalcaemic seizures in the BPSU study required admission to hospital, for a median duration of 3 days, and many required treatment with medications such as intravenous calcium gluconate which are associated with a risk of complications. Children with rickets commonly experience debilitating symptoms such as chronic musculoskeletal pain, skeletal deformity, and delay in gross motor development.

Whilst uncommon, symptomatic vitamin D deficiency is inherently preventable, provided that individuals either synthesise sufficient vitamin D endogenously in the skin through adequate sunlight exposure, or have adequate intake of vitamin D from fortified foods or supplements. The results from the BPSU surveillance study, and from the regional UK studies identified in the systematic review, suggest that the current implementation of public health policy in the UK is not effective in preventing children from developing significant clinical complications of vitamin D deficiency. Public health policy in this area should be reviewed and reconsidered, with the aim of achieving a reduction in the incidence of symptomatic vitamin D deficiency in children.

The current public health approach regarding the prevention of vitamin D deficiency in the UK is based upon the recommendation of vitamin D supplementation for high-risk population groups (see chapter 2.8). Although the Department of Health (DoH) recommends that prophylactic vitamin D supplements are taken by all pregnant and lactating women, and all children from birth to 5 years who consume less than 500ml of infant formula milk per day, in most areas of the country supplements are provided free of charge only to low-income families through the Healthy Start scheme. Uptake rates for Healthy Start vitamins among eligible families have been reported to be very low (<10%) across the country (Jessiman et al, 2013; Moonan et al, 2012). Reasons that

have been suggested for the poor uptake of Healthy Start vitamins include poor accessibility with limited distribution points for the vitamins, a lack of awareness among eligible families, and poor promotion of the scheme by healthcare professionals (Jessiman et al, 2013). The overall use of vitamin supplements, whether Healthy Start or other brands, by children in the general population is also low, with only 9% to 14% of breastfed infants aged <1 year receiving vitamin drops (McAndrew et al, 2012). Knowledge regarding the DoH recommendations for vitamin D supplementation among various groups of health professionals involved in the care of pregnant women and young children, as well as among parents, has been shown to be limited (Cleghorn, 2006; Jain et al, 2011; Sharma et al, 2011; Zipitis et al, 2011).

In order for a prevention policy based upon vitamin D supplementation to be effective, it is clear that the uptake of supplements among pregnant women and children needs to be considerably higher than current rates. One approach that has been suggested to achieve this is to move from a policy of targeted provision of supplements based upon income, to universal provision of supplements to all pregnant women and young children. In response to a recommendation from the Child Medical Officer for England (Lemer, 2013), the DoH commissioned the National Institute for Health and Care Excellence (NICE) to examine the cost effectiveness of moving the Healthy Start vitamin programme from the current targeted offering to a universal scheme (NICE, 2015). However, the analysis was limited by a lack of quality of life data for vitamin D deficiency, which meant that quality-adjusted life years (QALYs) could not be assigned to the effects of vitamin D supplementation in the model. As a result of this, the impact of folic acid supplementation had a dominant effect on the results of the cost-effectiveness modelling. Folic acid is contained in the Healthy Start vitamin tablets for women, and supplementation prior to and during the early stages of pregnancy considerably reduces the risk of neural tube defects in offspring. QALY data was available for the most common type of neural tube defect, spina bifida. The results suggested that universal provision of Healthy Start vitamins could be cost effective, with an estimated incremental cost-effectiveness ratio (ICER) of £6,528 per QALY gained, provided that the scheme was extended to include women planning pregnancy and those less than 10 weeks pregnant, due to a reduction in children born with neural tube defects. NICE uses an ICER threshold range of between £20,000 to £30,000 per QALY gained for the assessment of the cost-effectiveness of healthcare interventions (McCabe et al, 2008). In view of the absence of health utility data for vitamin D deficiency, it was not possible for the authors to specifically model the cost-effectiveness of universal provision of vitamin D supplements.

In a limited number of areas of the UK, local schemes have been introduced to make free of charge Healthy Start vitamin supplements universally available for all pregnant and lactating women and young children. One such programme was introduced in the Heart of Birmingham Primary Care Trust catchment area, in inner-city Birmingham, in 2006 (Moy et al, 2012). Families were given an initial bottle of vitamins by their health visitor at the time of the first new baby home visit at 2 to 4 weeks of age, however they were required to obtain further bottles from certain issuing sites (health centres, children's centres, and some community pharmacies and GP practices). In addition, the programme involved education of health care staff involved in the care of pregnant women and children, and targeted dissemination of information to the public through local media networks and Asian food retailers. The scheme achieved modest increases in uptake rates of Healthy Start vitamin supplements. Between 2 years (2008-2009) to 6 years (2012-2013) after the introduction of the programme, uptake rates of children's supplements increased from 7% to 20%, and of women's supplements from 4% to 23% (McGee & Shaw, 2013). However, the impact of the publicity campaign on the uptake of other over the counter vitamin supplements could not be assessed.

Assessment of a programme providing free vitamin D supplements to infants aged <1 year in Quebec, which started in 1997, also reported low uptake rates (Millette et al, 2014). The scheme included all infants covered by a public medication insurance programme, and the vitamin D supplements could only be obtained through prescription by a physician. Between 1998 to 2008, the average uptake rate for supplements by eligible families was only 17.9%.

The assessment of the impact of the Birmingham and Quebec schemes suggests that the universal free availability of vitamin supplements is unlikely, on its own, to achieve high uptake rates. The methods of distribution and accessibility of the vitamin supplements are likely to have an important influence on uptake rates. In both of the above schemes, parents were required to proactively collect or request the vitamin supplements from issuing sites. It has been recommended that the distribution of vitamin D supplements should be incorporated into existing antenatal and childhood health care programmes (Munns et al, 2016), and this is one possible method by which supplementation schemes may achieve higher uptake rates. Qualitative research has suggested that parents are most likely to use Healthy Start vitamins if they are handed out directly by healthcare professionals, rather than when parents are required to collect them from distribution points (Jessiman et al, 2013). Consideration should be given to developing public health initiatives for vitamin D deficiency prevention which involve the universal free of charge distribution of vitamin supplements to pregnant

women and young children through existing NHS health care programmes. These could include routine antenatal care appointments, routine newborn physical examinations (shortly after birth, and at 6 to 8 weeks of life), routine childhood immunisation appointments, and routine health visitor appointments. Uptake rates for these established health care programmes are relatively high, for example 93% of infants in the UK complete the course of recommended immunisations in the first year of life (PHE, 2017), and uptake rates for health visitor appointments range from 88% at the new birth visit to 75% at the 2 to 2½ year review (PHE, 2016).

NICE has undertaken a review to identify evidence-based approaches to increasing the use of vitamin D supplements among at-risk groups (NICE, 2014). Although the overall quality of the evidence base was considered to be poor (Morgan et al, 2014), the report made several recommendations for increasing vitamin D supplement uptake:

i) Increasing accessibility of vitamin D supplements, including Healthy Start vitamins, by ensuring that low cost supplements are more widely distributed, sold, and promoted. Increasing the range of settings where supplements are available to include local pharmacies and supermarkets, children's centres, midwifery and health vising services, GP practices, and schools.

ii) Developing national and local activities to increase the population's awareness of vitamin D, its importance for health, and advice regarding supplement use.

iii) Consideration of providing vitamin supplements free of charge to all pregnant and breastfeeding women, and children aged under 5 years.

iv) Education of health and social care professionals regarding the importance of vitamin D and national supplementation recommendations.

v) Ensuring that health care professionals recommend vitamin D supplement use to relevant population groups during routine appointments.

The age distribution of cases of hypocalcaemic seizures observed in the BPSU surveillance study, with the majority under 6 months (57%), supports the recent change in DoH guidance regarding vitamin D supplementation for this age group. Prior to the publication of updated recommendations by the Scientific Advisory Committee on Nutrition (SACN) regarding dietary reference values for vitamin D (SACN, 2016), DoH guidelines did not recommend routine vitamin D supplements for infants under 6 months of age (DoH, 2009). However, in line with the recent recommendations by SACN, current DoH advice recommends that all breastfed babies should take a daily

supplement containing between 8.5 to 10mcg (300 to 400 units) of vitamin D (DoH, 2016).

A significant proportion of children with hypocalcaemic seizures identified in the BPSU study were neonates under one month of age (26%). More than half of the cases presenting as neonates were reported to be exclusively formula milk fed (54%). These results suggest that the vitamin D content of formula milk alone is not sufficient to prevent severe manifestations of vitamin D deficiency developing in neonates born to mothers with suboptimal vitamin D status during pregnancy, and highlights the importance of vitamin D supplementation during pregnancy in order to ensure adequate vitamin D status in newborns. It also questions whether current guidance that formula-fed infants do not require additional vitamin D supplementation is appropriate, particularly in cases where mothers have not taken supplements during pregnancy. Any public health initiatives that are developed with the aim of preventing symptomatic vitamin D deficiency in children must involve maternity as well as child health services, as infants born to mothers with severe vitamin D deficiency can develop clinical complications of hypocalcaemia very soon following birth, before post-natal interventions such as supplementation can have effect.

## 7.4 Implications for Health Services and Clinical Practice

In the BPSU surveillance study of hypocalcaemic seizures secondary to vitamin D deficiency, a minority of cases (13%) did not receive vitamin D replacement in the form recommended by UK and international guidelines (treatment dose colecalciferol or ergocalciferol). This suggests that the knowledge of guidelines regarding the treatment of vitamin D deficiency among paediatricians could be improved. The publication of guidance regarding vitamin D (RCPCH, 2013), and the development of an e-learning module (RCPCH, 2014), by the Royal College of Paediatrics and Child Health may help to address this.

The cohort studies undertaken using the THIN database demonstrated that there has been a marked increase in the testing and diagnosis of vitamin D deficiency among children in UK clinical practice over the last decade, and that the cost implications of this change in clinicians' diagnostic behaviour for the health service are not insignificant.

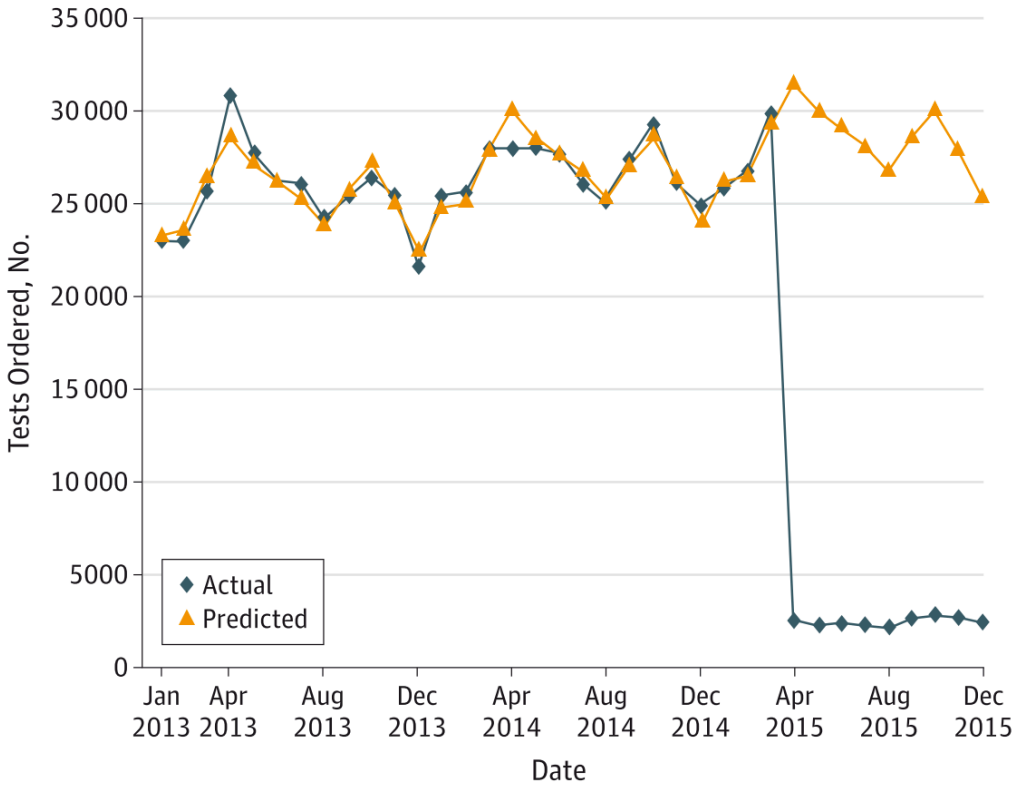
Given the magnitude of the increase in diagnosis over a relatively short period of time (15-fold between 2008 to 2013), it is highly unlikely to be explained by changes in population vitamin D levels, incidence of clinical complications of vitamin D deficiency, or population demographics. It is likely that the rise in testing and treatment has been driven by increased awareness and consideration of vitamin D deficiency among clinicians. There are several possible contributing factors for this: clinician education through the development of clinical guidelines and dissemination of Department of Health recommendations concerning vitamin D supplementation for high risk groups (Davies et al, 2012; DoH, 2009), reports of a rise in cases of rickets among children in the UK (Ahmed et al, 2011; Allgrove, 2004; Davies & Shaw, 2011; Shaw & Pal, 2002), and wide reporting in the general media and medical literature of research suggesting a link between vitamin D status and numerous non-musculoskeletal health outcomes (Harvey & Cooper, 2012; Holick, 2007; Pearce & Cheetham, 2010).

The data available did not permit meaningful exploration of the reasons prompting investigation of vitamin D status among children in clinical practice. Therefore, it was not possible to determine how much the increase in diagnosis has been driven by improved recognition of children with symptomatic vitamin D deficiency, or by testing of vitamin D status in other clinical situations (for example screening of asymptomatic children, testing in children with non-specific symptoms, or testing prompted by the presence of non-musculoskeletal diseases that have been linked to vitamin D deficiency such as diabetes, atopic disorders, and infectious diseases).

However, comparison of the observed rates of diagnosis of vitamin D deficiency with available incidence estimates for symptomatic complications of deficiency (see section 7.2.1), suggests that considerably more children are currently being diagnosed with vitamin D deficiency than those who develop its recognised clinical complications. Whilst rates of diagnosis observed prior to 2008 (below 10 per 100,000 PYAR) were broadly comparable to available incidence estimates for symptomatic deficiency of between 2.2 to 7.5 per 100,000 children per year, it is clear that the rates of diagnosis in more recent years (over 200 per 100,000 PYAR in 2013 and 2014) were considerably higher than this. Furthermore, whilst symptomatic complications of vitamin D deficiency occur most frequently in young children in the first 3 years of life, overall rates of diagnosis of vitamin D deficiency were significantly higher among older children aged ≥10 years. This observation suggests that vitamin D testing and diagnosis among children in clinical practice is unlikely to be primarily focused upon individuals with recognised clinical complications of deficiency such as rickets and hypocalcaemia.

Insights may also be drawn from studies involving adult populations. In response to an increase in the number of vitamin D test requests being received by clinical pathology laboratories in Alberta, Canada, a province-wide change in test ordering procedures was introduced in April 2015 (Ferrari & Prosser, 2016). From that point on, a defined set of clinical criteria permitting 25-OH-D testing was introduced, and orders were only processed if one of the following indications was specified on the test request: metabolic bone disease, abnormal calcium level, malabsorption syndrome (e.g. coeliac disease, small-intestinal surgery, anticonvulsant agent), chronic renal disease, or liver disease. This resulted in a 92% reduction in the number of tests ordered (Figure 7.1), and annual cost savings of almost 4 million US dollars.

**Figure 7.1** 25-OH-D test requests received by Alberta Health Services in Canada, before and after the introduction of a defined set of clinical criteria permitting 25-OH-D testing in April 2015.[a]




Abbreviations: 25-OH-D, 25-hydroxyvitamin D.
[a] The blue diamonds represent the actual number of 25-OH-D test requests received, whilst the orange triangles represent the predicted number of test requests based on historical data. Source: Ferrari & Prosser (2016).

These results suggest that, prior to the intervention, the majority of vitamin D tests were performed in individuals without specific clinical features or risk factors for deficiency. A similar response was seen after the introduction of a policy recommending targeted vitamin D testing among adults in Australia (Boyages, 2016), which advised that testing should only be undertaken in the following 'high-risk' groups: patients with osteoporosis, osteomalacia, disorders of calcium and parathyroid hormone, malabsorption, chronic renal disease, individuals with darker pigmented skin or reduced sun exposure, children under 16 years of age, and patients taking drugs known to reduce vitamin D levels. Following the introduction of the national policy in November 2014, there was a 42% reduction in healthcare expenditure on vitamin D tests over the subsequent 8 months compared to the same period in the preceding year.

Although further studies are required to directly explore the reasons for investigation of vitamin D status in children in clinical practice, the observations described above suggest that is it unlikely that testing is focused upon children with recognised clinical complications of deficiency. Biochemical vitamin D deficiency, as defined by current guidelines, has a high prevalence in the general population, and testing in any patient group is likely to identify a significant proportion of abnormal results (see chapter 2.7.1). The choice of threshold 25-OH-D levels used to define deficiency varies across guidelines internationally and has a limited evidence base in children (see chapter 2.4). Whilst the benefits of treatment with pharmacological doses of vitamin D are clear in children with symptomatic deficiency, there is no evidence that testing and treating asymptomatic individuals results in improved health outcomes compared with prophylaxis with low-dose supplements (SACN, 2016; Shaw & Mughal, 2013b).

For these reasons, the UK Institute for Health and Care Excellence (NICE, 2014), US Endocrine Society (Holick et al, 2011), European Academy of Paediatrics (Grossman et al, 2017), and international paediatric consensus recommendations (Munns et al, 2016) have all advised against the routine screening of vitamin D status. Authors have suggested that the primary reasons for requesting vitamin D measurement in children should relate to relate to symptoms and signs relating to the effects of vitamin D on the skeleton or muscle function (Shaw & Mughal, 2013b). A set of clinical indications for the measurement of 25-hydroxyvitamin D in children that has been proposed is shown in Table 7.1.

**Table 7.1** Proposed clinical indications for the measurement of 25-hydroxyvitamin D in children.[a]

| |
|---|
| **Symptoms and signs of rickets / osteomalacia** |
| • Progressive bowing deformity of legs |
| • Waddling gait |
| • Abnormal knock knee deformity (intermalleolar distance >5 cm) |
| • Swelling of wrists and costochondral junctions (rachitic rosary) |
| • Prolonged bone pain (>3 months duration) |
| **Symptoms and signs of muscle weakness** |
| • Delayed walking |
| • Difficulty climbing stairs |
| • Cardiomyopathy in an infant |
| **Abnormal bone profile or x-rays** |
| • Low plasma calcium or phosphate |
| • Raised alkaline phosphatase |
| • Osteopenia or changes of rickets on x-ray |
| • Pathological fractures |
| **Disorders impacting on vitamin D metabolism** |
| • Chronic renal failure |
| • Chronic liver disease |
| • Malabsorption syndromes, e.g. cystic fibrosis, Crohn's disease, coeliac disease |
| • Older anticonvulsants, e.g. phenobarbitone, phenytoin, carbamezapine |
| **Children with bone disease in whom correcting vitamin D deficiency prior to specific treatment would be indicated** |
| • Osteogenesis imperfecta |
| • Idiopathic juvenile osteoporosis |
| • Osteoporosis secondary to glucocorticoids, inflammatory disorders, immobility |

[a] Source: Shaw & Mughal (2013b).

At the individual level, testing outside of this context requires careful consideration of whether vitamin D deficiency is related to the child's presentation or is a coincidental finding. It also represents exposure of children to an unnecessary painful procedure without any clear benefit in terms of improving clinical management or health outcomes. From a health services perspective, unnecessary testing results in avoidable healthcare expenditure, with costs arising from the tests themselves, and from subsequent prescription of pharmacological doses of vitamin D and from follow-up consultations.

The identification of potential sources of cost savings, without adversely impacting upon patient care and health outcomes, is of increasing importance in the current climate of significant financial constraints in the National Health Service (NHS) (Iacobucci, 2017). On the basis of currently available evidence (SACN, 2016), the testing and treatment of vitamin D deficiency in asymptomatic individuals falls into this category. In view of the magnitude of the observed increase in diagnosis of vitamin D deficiency, and in healthcare spending on vitamin D tests and prescriptions, among children in clinical practice over the last decade, there is likely to be scope to significantly reduce expenditure if testing is limited to individuals with specific clinical indications (Table 7.1). The size of potential cost savings is not insignificant if adult practice is also considered; vitamin D prescriptions accounted for 1% (£92 million) of the total NHS expenditure on prescriptions issued by community pharmacies in England in 2014 (HSCIC, 2015b).

Avoidance of routine screening of vitamin D levels is advocated by the Choosing Wisely campaigns in the USA (http://www.choosingwisely.org, accessed 21/08/2017), Canada (http://www.choosingwiselycanada.org, accessed 21/08/2017), and Australia (http://www.choosingwisely.org.au, accessed 21/08/2017). However, routine vitamin D testing was not included among the initial list of low value investigations and treatments compiled for the UK Choosing Wisely initiative led by the Academy of Medical Royal Colleges (http://www.choosingwisely.co.uk, accessed 21/08/2017). Given the large increase in testing observed among children in UK clinical practice over the last decade, untargeted vitamin D testing should be considered for inclusion in the UK Choosing Wisely campaign. NHS primary and secondary care services in the UK should consider the introduction of criteria-based approaches to limiting excessive vitamin D testing, as have been successfully implemented in Alberta, Canada (Ferrari & Prosser, 2016).

## 7.5 Recommendations for Future Research

The systematic review described in chapter 3 identified that the existing literature regarding the incidence of symptomatic vitamin D deficiency in children is limited in terms of the number, geographical coverage, and quality of existing studies. The number of studies considered to be of higher methodological quality was small (six), and provided data from only four countries (Canada, Denmark, New Zealand, and the UK). In order to minimise the risk of bias, future studies that are designed to investigate

the epidemiology of symptomatic vitamin D deficiency should have a clear case definition (to reduce the risk of case misclassification), should ascertain cases presenting to both outpatient and inpatient healthcare services and ideally from primary as well as secondary care (to reduce case under ascertainment), and should have national coverage so as to generate findings that are generalizable to the population as a whole. Future studies should report results stratified by age, sex, and ethnicity, which few existing studies have done, so that socio-demographic differences in the incidence of symptomatic vitamin D deficiency can be better understood.

Existing studies are largely limited to high-income countries with predominantly Caucasian populations. Data is lacking from many regions of the world, including Africa, Asia, the Middle East, and South America. Future studies should address this gap in epidemiological evidence from low- and middle-income countries (LMIC). Undertaking studies which can provide reliable data regarding disease incidence in many LMIC is likely to be challenging, as existing mechanisms for prospective disease surveillance or the prospective collection of routine healthcare data may not exist. As dietary calcium deficiency is an important cause of rickets in many LMIC, studies conducted to investigate symptomatic vitamin D deficiency in these settings must include biochemical assessment, and ideally also assessment of dietary intake, in order to distinguish the relative contribution of vitamin D deficiency and dietary calcium deficiency in the aetiology of disease.

Although anecdotal reports and local case series have raised concerns that symptomatic vitamin D deficiency may have increased in frequency among children in high-income countries in recent decades, data from existing studies are insufficient to draw any conclusions regarding temporal trends in incidence over the last 25 years. Consideration should be given to designing future studies with longer study periods, of at least 10 years, in order to investigate temporal trends in incidence and offer insight into the impact of any future changes in public health policy. This could be achieved through long-term prospective surveillance, such as the ongoing surveillance of perinatal HIV exposure and paediatric HIV infection undertaken by the British Paediatric Surveillance Unit (BPSU) and Royal College of Obstetricians and Gynaecologists since 1989 (Gibb et al, 2003). In countries where comprehensive healthcare administrative data records are available for research purposes, such as in various Scandinavian countries and records from large healthcare providers in the US, temporal trends in the incidence of symptomatic vitamin D deficiency could be investigated using existing data sources.

The BPSU surveillance study described in chapter 4 is the first study in the UK to report national incidence estimates for any of the clinical manifestations of vitamin D deficiency. However, it is limited to hypocalcaemic seizures, and captures only part of the health burden caused by vitamin D deficiency in childhood. Further studies are required to evaluate the epidemiology of symptomatic vitamin D deficiency more broadly in the UK. A separate BPSU study of nutritional rickets presenting to secondary care has recently been undertaken, with a 2-year surveillance period between March 2015 to March 2017. The final results from the study have not yet been published, however preliminary data indicated that 59 confirmed cases were identified in the first 13-months of surveillance (Julies & Blair, 2016). Based upon the findings of previous case series, musculoskeletal features of rickets and hypocalcaemic seizures represent the two most common modes of presentation of children to secondary care services with symptomatic vitamin D deficiency (see chapter 2.7.2). Taken together, the results from both BPSU surveillance studies will provide a reasonably comprehensive assessment of the incidence of symptomatic vitamin D deficiency presenting to paediatric secondary care services in the UK. It is likely that all children with acute presentations such as seizures, and the majority of children with rickets, will be referred to paediatric services. However, these studies will not capture children with more subtle symptoms, such as older children with non-specific musculoskeletal pain and muscle weakness, who may be managed in primary care. Future studies should attempt to investigate the burden of symptomatic vitamin D deficiency among children in primary care.

The cohort study described in chapter 5 demonstrated that there has been a marked increase in the diagnosis of vitamin D deficiency among children in UK clinical practice over the last decade. Future research should be undertaken to explore the drivers for this change in clinician's diagnostic behaviour. Studies should investigate the reasons prompting investigation of vitamin D status among children in clinical practice, and determine the extent to which testing is focused on children with clinical features consistent with symptomatic vitamin D deficiency, compared to the screening of vitamin D status in asymptomatic children. Both quantitative and qualitative methodologies would help to answer this research question. Studies should be undertaken in both primary care as well as secondary care, as the clinical indications for testing are likely to differ across these settings.

The cohort study described in chapter 6 explored the economic implications of the increase in diagnosis of vitamin D deficiency, with respect to expenditure on vitamin D tests and prescriptions for children in primary care. Further work is required to

investigate other related costs which could not be ascertained by this study, including costs related to healthcare episodes such as GP consultations, and expenditure arising in secondary care. Future studies should also explore trends in the diagnosis of vitamin D deficiency, and associated healthcare costs, in adult practice, where the overall magnitude of expenditure is likely to be considerably greater than in children's care.

Should any health service interventions be introduced in the UK with the aim of limiting excessive vitamin D testing, as have been recently developed in Canada and Australia, their impact should be prospectively evaluated.

Further research is necessary to identify effective interventions for increasing the uptake of vitamin D supplements among key population groups including pregnant women and young children, particularly those from high-risk ethnic backgrounds. The design of such interventions should incorporate evaluation of their cost-effectiveness. In order for the cost-effectiveness of public health interventions aimed at prevention of vitamin D deficiency to be evaluated, studies are required to determine the health utility impact (in terms of QALYs) of complications of vitamin D deficiency in childhood.

## 7.6 Conclusion

The studies described in this thesis have advanced knowledge regarding the epidemiology of symptomatic vitamin D deficiency in UK children, regarding the diagnosis of vitamin D deficiency in children in clinical practice, and regarding the economic implications of changes in clinical practice over the last 15 years. As vitamin D has become a 'hot topic', and generated considerable academic and clinical interest over the last two decades, the investigation and diagnosis of vitamin D deficiency among children in clinical practice has increased considerably, with important economic implications for the health service. However, despite this increased level of interest, children in the UK are continuing to develop significant, and preventable, clinical complications of vitamin D deficiency. When considered in the context of the existing literature, the results from this thesis suggest that vitamin D deficiency may be being over-tested and over-diagnosed, yet under-prevented, among children in the UK. These findings have implications for public health policy, clinical practice and health service delivery, and help to inform areas for future research.

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# Appendix A: Publications and Presentations Arising from the Work Described in the Thesis

## A.1 Publications

1. Basatemur E, Sutcliffe A. Incidence of hypocalcemic seizures due to vitamin D deficiency in children in the United Kingdom and Ireland. *Journal of Clinical Endocrinology and Metabolism*. 2015;100(1), E91-5

2. Basatemur E, Horsfall L, Marston L, Rait G, Sutcliffe A. Trends in the diagnosis of vitamin D deficiency. *Pediatrics*. 2017;139(3):e20162748

3. Basatemur E, Hunter R, Horsfall L, Sutcliffe A, Rait G. Costs of vitamin D testing and prescribing among children in primary care. *European Journal of Pediatrics*. 2017; doi:10.1007/s00431-017-2986-9

## A.2 National and International Presentations

1. Basatemur E, Sutcliffe A. Surveillance of hypocalcaemic seizures secondary to vitamin D deficiency in children in the UK. Oral presentation. RCPCH Annual Conference, Glasgow, 7th June 2013.

2. Basatemur E, Sutcliffe A. National surveillance study of hypocalcaemic seizures secondary to vitamin D deficiency in children in the UK. Poster presentation. Vitamin D and Human Health Conference, Queen Mary University, London, 23rd April 2014.

3. Basatemur E, Horsfall L, Rait G, Sutcliffe A. Trends in the Diagnosis of Vitamin D Deficiency in UK Children between 2000-2014. Oral presentation. Academic Paediatric Association (APA) Conference, Liverpool, 15th April 2016.

4. Basatemur E, Horsfall L, Rait G, Sutcliffe A. Trends in the Diagnosis of Vitamin D Deficiency in UK Children Between 2000-2014. Oral presentation. Pediatric Academic Societies (PAS) Conference, Baltimore, US, 2nd May 2016.

## Appendix B: Ethical and Regulatory Approvals

B.1 Ethics approval for the BPSU study …….. 277

B.2 NIGB approval for the BPSU study ……... 280

B.3 BPSU Executive Committee approval for the BPSU study ……... 282

B.4 Scientific Review Committee approval for the THIN study …… 285

# B.1 Ethics Approval for the BPSU study

**NRES Committee London - Central**
Level 7N019, Maternity Block
Northwick Park Hospital
Watford Road
Harrow
Middx
HA1 3UJ

Telephone: 020 8869 3775
Facsimile: 020 8869 5222

05 July 2011

Dr Emre Basatemur
NIHR Academic Clinical Fellow in Paediatrics
Institute of Child Health, University College London
General and Adolescent Paediatric Unit, Institute of Child Health,
University College London,
30 Guilford Street, London
WC1N 1EH

Dear Dr Basatemur

| | |
|---|---|
| **Study title:** | **British Paediatric Surveillance Unit Study of Hypocalcaemic Seizures due to Vitamin D Deficiency in Children** |
| **REC reference:** | **11/LO/0838** |
| **Protocol number:** | **1.0** |

The Research Ethics Committee reviewed the above application at the meeting held on 29 June 2011. Thank you for attending to discuss the study.

**Ethical opinion**

The committee found no ethical issues with this study.

In discussion, the Committee found no ethical issues, and were pleased to see that the researcher had decided to contact charities to help disseminate future research findings.
Members felt that the researcher was highly qualified and agreed that his application was well written and worthwhile.

The Chair conveyed this to Dr Basatemur who was waiting in the adjoining room.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

**Ethical review of research sites**

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Approved documents**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering Letter | | 21 May 2011 |
| Evidence of insurance or indemnity | | |
| Investigator CV | | |
| Other: Academic Supervisors CV | | 01 September 2010 |
| Other: Data protection register details | | 21 May 2011 |
| Other: public Information sheet | 1 | 24 May 2011 |
| Other: case notification form | 1 | 24 May 2011 |
| Other: certificate from Sir P Tizard Research Bursary | | |
| Other: Letter from British Paediatric Surveillance Unit | | 11 October 2010 |
| Other: Letter from British Paediatric Surveillance Unit | | 27 July 2010 |
| Other: email from Professor Alan Emond | | 25 January 2011 |
| Other: System Level Security Policy/appendix 1 | 1 | 24 May 2011 |
| Protocol | 1 | 28 March 2011 |
| Questionnaire: Follow up questionnaire | 1 | 24 May 2011 |
| REC application | | 19 May 2011 |

**Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments

- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

| | |
|---|---|
| **11/LO/0838** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project

Yours sincerely

**Dr John Keen**
**Chair**

Email: Julie.kidd@nwlh.nhs.uk

| | |
|---|---|
| *Enclosures:* | *List of names and professions of members who were present at the meeting and those who submitted written comments*<br><br>*"After ethical review – guidance for researchers"* |

| | |
|---|---|
| *Copy to:* | *Nima Sharma, UCL - Institute of Child Health* |

## B.2 NIGB Approval for the BPSU study

NIGB

**Ethics and Confidentiality Committee**

*NHS Connecting for Health,*
*Floor 7,*
*New Kings Beam House,*
*22 Upper Ground,*
*London,*
*SE1 9BW.*
*Tel: (020) 7633 7052*

Dr Emre Basatemur
Institute of Child Health, University College London
General and Adolescent Paediatric Unit
University College
30 Guilford Street
London
WC1N 1EH

15 July 2012

Dear Dr Basatemur

**ECC/BPSU 6-02(FT7)/2011 Hypocalcaemic Seizures Due To Vitamin D Deficiency In Children**

Thank you for your application for support under section 251 of the NHS Act 2006 and the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process patient identifiable information without consent. This application followed the British Paediatric Surveillance Unit (BPSU) methodology and was therefore processed via the fast track procedure.

**Application context**

This application detailed a study using the BPSU orange card methodology in order to provide the incidence of hypocalcaemic seizures due to vitamin D deficiency in infants and children in the UK and Ireland. NHS Number, Hospital ID, date of birth, date of death and sector level postcode were required for de-duplication purposes and date of birth, date of death and sector level postcode would be retained for analysis purposes.

**Outcome**

The Committee agreed to recommend provisional approval under section 251 to this application. The Committee specified the following conditions of approval:

1. The provision of a favourable REC opinion (received 8/7/2011)
2. Confirmation of satisfactory security arrangements (approved 12/7/2011)

As these conditions have been met this constitutes your final approval letter. I will arrange for our register of approved applications on our website to be updated shortly with details of your application.

**Annual Review**

Please note that your approval under section 251 is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of this final approval letter and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. Please ensure that this is received approximately

NIGB

**Ethics and Confidentiality Committee**

8 weeks prior to this submission deadline. If section 251 support is no longer required prior to this please provide a report confirming all patient identifiable data has been destroyed.

Please do not hesitate to contact me if you have any queries following this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
Deputy Approvals Manager

# B.3 BPSU Executive Committee approval for the BPSU study

PATRON
HRH The Princess Royal

**Royal College of Paediatrics and Child Health**
**5-11 Theobalds Road WC1X 8SH**
*Telephone: 0207 092 6173/74 Fax: 0207 092 6001 E-mail:enquiries@rcpch.ac.uk*

Dr Emre Basatemur
Academic Clinical Fellow
General & Adolescent Unit
UCL Institute of Child Health
30 Guilford St
London WC1N 1EH

11th October 2010

Dear Emre,

**RE: Phase 2 Application – Hypocalcaemic Seizures Secondary to Vitamin D Deficiency**

Thank you very much for submitting your Phase 2 application to the BPSU Executive Committee meeting of 30th September 2010. Members of the committee were very interested to talk with you about your proposal and were pleased to be able to congratulate you in person on winning the Sir Peter Tizard Bursary for 2010.

Committee members discussed your Phase 2 application and supporting documentation in some detail and were grateful to you and Dr Sutcliffe for answering questions on your proposal. After deliberation, committee members considered that your Phase 2 application could be approved by Chair's action if the following amendments, discussed with you at the meeting, were made to the study protocol, questionnaires and public information sheet:

**Study protocol**

1. Members suggested that the 'background' to the study could more clearly cite the NICE antenatal care guidelines in respect of known higher risk subgroups. In addition, the reference to Afro-Caribbean as an ethnic subgroup should be changed to African-Caribbean or African as these are terms used in census classifications. Moreover, vitamin D deficiency is more often a concern in UK populations of African rather than Caribbean origin.
2. The statement that fits cause long-term problems with 'brain function' in the lay summary be removed or amended as this is not sufficiently accurate as currently written and may be unduly alarming to lay readers.
3. The study objectives should be amended to state that serum Vitamin D and calcium levels will be 'described' rather than, as currently implied, that 'levels at which fits occur' will be defined. As discussed with you, members felt that defining a threshold for seizures would not be possible using observational data.

4. Committee members asked points 1 and 2 in the sectionof the case definition headed 'Exclusions' should be removed from the reporting case definition and placed within the analytic case definition where they can be applied by the expert review panel.

**Public information sheet**

1. The public information sheet currently includes a statement 'We hope that this study will provide us with important information about how many children are having fits as a result of vitamin D deficiency.' It was felt by lay members that this was unduly alarming and perhaps should be omitted or changed to 'We hope that this study will provide us with important information about how common it is to have fits as a result of vitamin D deficiency.'

**Initial notification questionnaire:** The following specific changes were suggested:

1. Committee members suggested removal of the questions about who observed the seizure as they felt that answers to these would be difficult to interpret and were not relevant to the study objectives.
2. Postcode data are not available in Ireland and you may wish to ask for 'county of residence' instead. You may also wish to consider in what detail regional or postcode data will be required as this would presumably be as a guide to sunlight exposure. Collection of unnecessary postcode details should be avoided in order to protect the anonymity of children notified to the study.
3. Section C: You should clarify in Question 3.7 that you wish information on treatment at the first admission and not just at the time of the seizure as this may be otherwise misinterpreted.
4. Section D: Long QT syndrome has recently been reported in a case series involving London infants with vitamin D deficiency (Daubeney) and it was suggested that you should include a question about whether an ECG was performed and the results of this in Section D.
5. Section E: Committee members suggested that you add questions about parity, the use of sunscreens and maternal BMI to this section as maternal factors have significant impact on infant vitamin D levels at birth.
6. Section F: In Question 6.1, you should ensure that you are satisfied that you will collect sufficient detail for the panel to determine whether a notified case meets the exclusion criteria. In Question 6.2, it would be preferable to specify in a 'tick box' list some conditions that you are particularly interested in, e.g. neurological outcomes, developmental delay and rickets or skeletal abnormalities). You may also wish to include cardiomyopathy in this list as this is a recognised association with vitamin D deficiency.

**Follow-up questionnaire:** The following specific changes were suggested:

1. Committee members observed that Section B did not ask if the child had died, nor for the date and cause of death and suggested that this should be added as laid out in Section G of the initial questionnaire.
2. It was suggested that relevant sections of Section F (Question 6.1 and 6.2) could be included in the follow-up questionnaire also as sequelae of vitamin D deficiency may have become apparent in the months between completion of the first questionnaire and one year follow-up.

If you have any questions or concerns about these changes, then please contact Dr Rachel Knowles who will be happy to discuss these with you. Your final paperwork (including dated and revised versions of the Phase 2 application, public information sheet and questionnaires) should be sent to the BPSU Office at your convenience. Once this has been approved by Professor Alan Emond, a date for commencement of surveillance using the Orange Card will be arranged with you.

With kind regards,

Yours sincerely,

Dr Rachel Knowles, Senior Medical Adviser, BPSU

Professor Alan Emond, Chair, BPSU

cc. Mr Richard Lynn, BPSU Scientific Co-ordinator
Ms Helen Friend, BPSU Research Facilitator
Dr Alastair Sutcliffe, Consultant/Academic Supervisor

**British Paediatric Surveillance Unit (BPSU)**
A unit within the research division
Telephone: (020) 70926173/74 Fax: (020) 7092 6001
E-mail: bpsu@rcpch.ac.uk Website: http://bpsu.inopsu.com

## B.4 Scientific Review Committee approval for the THIN study

**SRC Feedback**

**Researcher Name:** Dr Emre Basatemur
**Organisation:** UCL
**SRC Reference Number:** 14-013
**Date:** 8th May 2014
**Study title: Childhood vitamin D deficiency in the UK: diagnosis, treatment and healthcare costs in primary and secondary care**
**Committee opinion:** Approved

---

**The following feedback has been supplied by the SRC.**

*Notes from the Chair:*

*Approved*

---

We are pleased to inform that you can proceed with the study as this is now approved. CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform CSD Medical Research in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Research Associate

# Appendix C: Detailed Search Strategies used in the Systematic Review

Table C.1 Search strategy used for the MEDLINE bibliographic database ……... 287

Table C.2 Search strategy used for the EMBASE bibliographic database …… 289

Table C.3 Search strategy used for the PsycINFO bibliographic database ……...291

Table C.4 Search strategy used for the CINAHL Plus bibliographic database …. 292

Table C.5 Search strategy used for the Web of Science bibliographic database.. 293

Table C.6 Search strategy used for the Global Health bibliographic database …. 293

**Table C.1** Search strategy used for the MEDLINE bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 1 | exp Vitamin D Deficiency/ | 24,196 |
| 2 | vitamin d deficiency.mp. | 16,349 |
| 3 | exp Rickets/ | 13,027 |
| 4 | rickets.mp. | 8,914 |
| 5 | rachit*.mp. | 1,776 |
| 6 | exp Osteomalacia/ | 4,635 |
| 7 | osteomalacia.mp. | 6,617 |
| 8 | hypovitaminosis d.mp. | 1,377 |
| 9 | avitaminosis d.mp. | 7 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 31,455 |
| 11 | exp Incidence/ | 221,915 |
| 12 | exp Prevalence/ | 240,123 |
| 13 | exp Epidemiology/ | 24,285 |
| 14 | incidence.mp. | 730,403 |
| 15 | prevalence.mp. | 579,035 |
| 16 | epidemiolog*.mp. | 411,315 |
| 17 | 11 or 12 or 13 or 14 or 15 or 16 | 1,528,512 |
| 18 | 10 and 17 | 5,511 |
| 19 | exp Vitamin D Deficiency/ep [Epidemiology] | 3,759 |
| 20 | exp Rickets/ep [Epidemiology] | 603 |
| 21 | exp Osteomalacia/ep [Epidemiology] | 131 |
| 22 | exp Child/ | 1,749,773 |
| 23 | child*.mp. | 2,192,212 |
| 24 | exp Infant/ | 1,053,667 |
| 25 | infant*.mp. | 1,160,013 |
| 26 | infancy.mp. | 57,548 |
| 27 | neonat*.mp. | 256,340 |
| 28 | newborn*.mp. | 701,293 |
| 29 | exp Adolescent/ | 1,835,172 |
| 30 | adolescen*.mp. | 1,893,314 |
| 31 | teenage*.mp. | 18,836 |
| 32 | toddler*.mp. | 8,497 |
| 33 | babies.mp. | 32,957 |
| 34 | baby.mp. | 33,597 |
| 35 | young person*.mp. | 3,102 |
| 36 | young people*.mp. | 22,370 |
| 37 | youth.mp. | 56,159 |
| 38 | exp Pediatrics/ | 52,874 |
| 39 | p?ediatric*.mp. | 324,473 |
| 40 | kid?.mp. | 6,992 |
| 41 | juvenile*.mp. | 81,622 |
| 42 | 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 | 3,930,286 |
| 43 | 18 and 42 | 1,933 |
| 44 | limit 18 to (“all infant (birth to 23 months)” or “all child (0 to 18 years)” or “newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)” or “child (6 to 12 years)” or “adolescent (13 to 18 years)”) | 1,491 |
| 45 | 43 or 44 | 1,933 |
| 46 | 19 or 20 or 21 or 45 | 4,772 |
| 47 | limit 46 to yr=”1990 – 2016” | **4,300** |

**Table C.1** continued.

[a] *exp* denotes a subject heading search, where the specified subject heading is 'exploded' to include the specified subject heading as well as any subheadings. *.mp.* denotes a free-text (or text-word) search. The following search fields were included for free-text searches: abstract, title, keyword, heading word, subject heading word, original title.

**Table C.2** Search strategy used for the EMBASE bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 1 | exp vitamin D deficiency/ | 24,276 |
| 2 | vitamin d deficiency.mp. | 25,567 |
| 3 | exp rickets/ | 9,414 |
| 4 | rickets.mp. | 10,767 |
| 5 | rachit*.mp. | 1,601 |
| 6 | exp osteomalacia/ | 8,771 |
| 7 | osteomalacia.mp. | 8,963 |
| 8 | hypovitaminosis d.mp. | 2,283 |
| 9 | avitaminosis d.mp. | 6 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 40,505 |
| 11 | exp incidence/ | 346,650 |
| 12 | exp prevalence/ | 669,917 |
| 13 | exp epidemiology/ | 2,949,552 |
| 14 | exp epidemiological data/ | 2,970,461 |
| 15 | incidence.mp. | 974,357 |
| 16 | prevalence.mp. | 821,261 |
| 17 | epidemiolog*.mp. | 1,413,009 |
| 18 | 11 or 12 or 13 or 14 or 15 or 16 or 17 | 4,526,352 |
| 19 | exp vitamin D deficiency/ep [Epidemiology] | 1,643 |
| 20 | exp rickets/ep [Epidemiology] | 364 |
| 21 | exp osteomalacia/ep [Epidemiology] | 117 |
| 22 | 10 and 18 | 14,052 |
| 23 | limit 22 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) | 3,110 |
| 24 | exp child/ | 2,563,197 |
| 25 | child*.mp. | 2,384,237 |
| 26 | exp infancy/ or exp infant/ | 1,023,619 |
| 27 | infant*.mp. | 819,883 |
| 28 | infancy.mp. | 61,317 |
| 29 | exp newborn/ | 546,079 |
| 30 | neonat*.mp. | 304,206 |
| 31 | exp pediatrics/ | 112,084 |
| 32 | newborn*.mp. | 638,437 |
| 33 | p?ediatric*.mp. | 492,298 |
| 34 | exp adolescence/ or exp adolescent/ or exp juvenile/ | 3,331,916 |
| 35 | adolescen*.mp. | 1,498,159 |
| 36 | teenage*.mp. | 24,237 |
| 37 | toddler*.mp. | 10,838 |
| 38 | babies.mp. | 43,353 |
| 39 | baby.mp. | 63,252 |
| 40 | young person*.mp. | 4,103 |
| 41 | young people*.mp. | 29,322 |
| 42 | youth.mp. | 58,848 |
| 43 | kid?.mp. | 9,410 |
| 44 | juvenile*.mp. | 142,013 |
| 45 | 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 | 3,972,513 |
| 46 | 22 and 45 | 4,217 |
| 47 | 23 or 46 | 4,217 |
| 48 | 19 or 20 or 21 or 47 | 5,329 |

**Table C.2** continued.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 49 | limit 48 to yr="1990 - 2016" | **4,901** |

[a] *exp* denotes a subject heading search, where the specified subject heading is 'exploded' to include the specified subject heading as well as any subheadings. *.mp.* denotes a free-text (or text-word) search. The following search fields were included for free-text searches: abstract, title, keyword, heading word, subject headings, original title.

**Table C.3** Search strategy used for the PsycINFO bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 1 | vitamin d deficiency.mp. | 420 |
| 2 | rickets.mp. | 101 |
| 3 | osteomalacia.mp. | 23 |
| 4 | hypovitaminosis d.mp. | 76 |
| 5 | avitaminosis d.mp. | 0 |
| 6 | rachit*.mp. | 26 |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 | 576 |
| 8 | exp epidemiology/ | 44,959 |
| 9 | incidence.mp. | 44,845 |
| 10 | prevalence.mp. | 96,103 |
| 11 | epidemiolog*.mp. | 85,787 |
| 12 | 8 or 9 or 10 or 11 | 186,212 |
| 13 | 7 and 12 | 188 |
| 14 | limit 13 to (childhood <birth to age 12 yrs> or neonatal <birth to age 1 mo> or infancy <2 to 23 mo> or preschool age <age 2 to 5 yrs> or school age <age 6 to 12 yrs> or adolescence <age 13 to 17 yrs>) | 22 |
| 15 | child*.mp. | 669,050 |
| 16 | infant*.mp. | 84,793 |
| 17 | infancy.mp. | 17,075 |
| 18 | exp neonatal period/ | 1,521 |
| 19 | exp pediatrics/ | 24,256 |
| 20 | neonat*.mp. | 19,183 |
| 21 | newborn*.mp. | 10,171 |
| 22 | p?ediatric*.mp. | 39,545 |
| 23 | adolescen*.mp. | 233,956 |
| 24 | teenage*.mp. | 12,640 |
| 25 | toddler*.mp. | 9,215 |
| 26 | babies.mp. | 5,686 |
| 27 | baby.mp. | 10,373 |
| 28 | young person*.mp. | 2,257 |
| 29 | young people*.mp. | 24,672 |
| 30 | youth.mp. | 77,960 |
| 31 | kid?.mp. | 4,284 |
| 32 | juvenile*.mp. | 33,200 |
| 33 | 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 | 899,070 |
| 34 | 13 and 33 | 51 |
| 35 | 14 or 34 | 53 |
| 36 | limit 35 to yr="1990 - 2016" | **47** |

[a] *exp* denotes a subject heading search, where the specified subject heading is 'exploded' to include the specified subject heading as well as any subheadings. *.mp.* denotes a free-text (or text-word) search. The following search fields were included for free-text searches: abstract, title, key concepts, table of contents, heading word, original title, tests & measures.

**Table C.4** Search strategy used for the CINAHL Plus bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| S1 | (MH "Vitamin D Deficiency+") | 5,471 |
| S2 | (MH "Rickets+") | 849 |
| S3 | (MH "Osteomalacia") | 295 |
| S4 | vitamin d deficiency | 5,660 |
| S5 | rickets | 822 |
| S6 | rachit* | 37 |
| S7 | osteomalacia | 469 |
| S8 | "hypovitaminosis-d" | 322 |
| S9 | avitaminosis-d | 126 |
| S10 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 | 6,729 |
| S11 | (MH "Incidence") | 44,793 |
| S12 | (MH "Prevalence") | 60,448 |
| S13 | (MH "Epidemiology+") | 478,871 |
| S14 | incidence | 116,890 |
| S15 | prevalence | 131,784 |
| S16 | epidemiolog* | 337,392 |
| S17 | S11 OR S12 OR S13 OR S14 OR S15 OR S16 | 739,322 |
| S18 | S10 AND S17 | 2,593 |
| S19 | limit S18 to SubjectAge: - infant, newborn: birth-1 month; - child, preschool: 2-5 years; - infant: 1-23 months; - all infant; - adolescent: 13-18 years: - child: 6-12 years: - all child | 765 |
| S20 | (MH "Child+") | 483,157 |
| S21 | (MH "Infant+") | 187,883 |
| S22 | (MH "Adolescence+") | 337,564 |
| S23 | (MH "Pediatrics+") | 14,961 |
| S24 | child* OR infant* OR infancy OR neonat* OR newborn OR p#ediatric* OR adolescen* OR teenage* OR toddler* OR babies OR baby | 4,488,879 |
| S25 | young person* OR young people* OR youth OR kid# OR juvenile* | 54,199 |
| S26 | S20 OR S21 OR S22 OR S23 OR S24 OR S25 | 4,490,259 |
| S27 | S18 AND S26 | 2,484 |
| S28 | S19 OR S27 | 2,484 |
| S29 | (MH "Vitamin D Deficiency+/EP") | 1,187 |
| S30 | (MH "Rickets+/EP") | 85 |
| S31 | (MH "Osteomalacia/EP") | 10 |
| S32 | S28 OR S29 OR S30 OR S31 | 2,531 |
| S33 | limit S36 to Publication Year: 1990-2016 | **2,481** |

[a] *MH* denotes a subject heading search, and the + symbol specifies that the subject heading is 'exploded' to include any subheadings. The following search fields were included for free-text searches: abstract, title, subject headings.

**Table C.5** Search strategy used for the Web of Science bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 1 | TS=("vitamin d deficiency") OR TS=(rickets) OR TS=(osteomalacia) OR TS=("hypovitaminosis d") OR TS=("avitaminosis d") | 20,807 |
| 2 | TS=(incidence) OR TS=(prevalence) OR TS=(epidemiolog*) | 1,399,181 |
| 3 | TS=(child*) OR TS=(infant*) OR TS=(infancy) OR TS=(neonat*) OR TS=(newborn*) OR TS=(babies) OR TS=(baby) OR TS=(toddler*) OR TS=(adolescen*) OR TS=(teenage*) OR TS=("young person*) OR TS=("young people*) OR TS=(youth) OR TS=(p$ediatric*) OR TS=(kid$) OR TS=(juvenile*) | 2,425,818 |
| 4 | #3 AND #2 AND #1 | **1,494** |

[a] The following search fields were included for free-text searches (*TS*): abstract, title, keywords. The search was limited to publications between 1990 to 2016.

**Table C.6** Search strategy used for the Global Health bibliographic database.

| Search No. | Search Query [a] | No. of Results |
|---|---|---|
| 1 | vitamin d deficiency.mp. | 5,098 |
| 2 | exp rickets/ | 5,585 |
| 3 | rickets.mp. | 6,187 |
| 4 | exp osteomalacia/ | 1,061 |
| 5 | osteomalacia.mp. | 1,536 |
| 6 | hypovitaminosis d.mp. | 652 |
| 7 | avitaminosis d.mp. | 8 |
| 8 | rachit*.mp. | 2,652 |
| 9 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 | 12,697 |
| 10 | exp incidence/ | 90,025 |
| 11 | incidence.mp. | 202,657 |
| 12 | exp disease prevalence/ | 125,197 |
| 13 | prevalence.mp. | 258,912 |
| 14 | exp epidemiology/ | 279,477 |
| 15 | epidemiolog*.mp. | 339,535 |
| 16 | 10 or 11 or 12 or 13 or 14 or 15 | 570,591 |
| 17 | 9 and 16 | 2,874 |
| 18 | exp childhood diseases/ | 1,294 |
| 19 | exp children/ | 286,033 |
| 20 | exp infants/ | 117,021 |
| 21 | exp neonates/ | 33,145 |
| 22 | exp paediatrics/ | 2,781 |
| 23 | exp adolescents/ | 48,751 |
| 24 | (child* or infant* or infancy or newborn* or neonat* or p?ediatric* or adolescen* or teenage* or toddler* or babies or baby or young person* or young people* or youth or kid? or juvenile*).mp. | 494,388 |
| 25 | 18 or 19 or 20 or 21 or 22 or 23 or 24 | 494,388 |
| 26 | 17 and 25 | 1,353 |
| 27 | limit 26 to yr="1990 - 2016" | **720** |

[a] *exp* denotes a subject heading search, where the specified subject heading is 'exploded' to include the specified subject heading as well as any subheadings. *.mp.* denotes a free-text (or text-word) search. The following search fields were included for free-text searches: abstract, title, broad terms, heading words, CABICODES, identifiers, original title.

# Appendix D: BPSU Study Documents

D.1 Cover letter to reporting clinicians…… 295

D.2 Data collection form……..296

*Name of Reporting Consultant*
*Department Name*
*Hospital Name*

*Date*

Dear Dr *Consultant Name*,

**Re: BPSU Study Investigating Hypocalcaemic Seizures Secondary to Vitamin D Deficiency**

Thank you very much for notifying us of a case for this study, which is being undertaken by the British Paediatrics Surveillance Unit at the RCPCH, and the UCL Institute of Child Health. We greatly value your contribution to the study.

We are writing to gather further information about your patient on the enclosed questionnaire. We would be very grateful if you could complete it and return it in the enclosed postage-paid envelope. **Please return the questionnaire, even if there are some sections you are unable to complete.** We anticipate that it will take around 10-15 minutes to complete, with the child's notes and laboratory results to hand when doing so.

The study is funded by the Sir Peter Tizard Bursary from the RCPCH. It has been approved by the Central London Research Ethics Committee and by the National Information Governance Board.

We will not be contacting your patient or his/her family at any time. Some patient identifiable data are needed to avoid duplication of reporting. These will be removed once the case has been confirmed to be a unique case, and all information you provide will be treated in strict confidence.

Please do not hesitate to contact us (details below) if you have any queries about the questionnaire, eligibility of a particular case for inclusion in the study, or any other aspect of the study. Further information about the study is also available online at www.rcpch.ac.uk/bpsu.

We are very grateful to you for reporting to the BPSU and for taking the time to provide further information about your patient.

Finally, we will also ensure that you are sent a copy of the final report of the study once it is completed.

With many thanks for your help,

Yours sincerely,

Dr Emre Basatemur
Academic Clinical Fellow
General & Adolescent Unit
UCL Institute of Child Health
30 Guilford Street, London WC1N 1EH
emre.basatemur@ucl.ac.uk
Tel: 07585227463

Dr Alastair Sutcliffe
Reader in Child Health
General & Adolescent Unit
UCL Institute of Child Health
30 Guilford Street, London WC1N 1EH
a.sutcliffe@ucl.ac.uk

## D.2 Data collection form

*For office use only:* ☐☐☐☐☐☐☐☐

**Case notification form - Strictly Confidential**

### Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

*Please contact Dr Emre Basatemur (0778 695 6113 / emre.basatemur@ucl.ac.uk) if you have any questions*

### Reporting Instructions:

Please report any child under 16 years of age who has had a first episode of a hypocalcaemic seizure secondary to vitamin D deficiency within the last month. Please report all suspected cases, even if the results of investigations are pending.

### Case Definition:

Any child under 16 years of age who develops a suspected seizure* in the presence of BOTH of the following biochemical criteria:

1. Low serum corrected calcium: < 2.0 mmol/L
2. Low serum 25-hydroxy vitamin D (25-OH-D) level: < 50 nmol/L (<20 ng/ml)

Excluding children with a history of a previous hypocalcaemic seizure due to vitamin D deficiency (prior to this presentation)

*Include cases where the event is felt to most likely represent a true seizure, as opposed to another paroxysmal event. A seizure can be defined as a paroxysmal, time-limited change in motor activity and/or behaviour that results from abnormal electrical activity in the brain.

### Section A: Reporter Details

**1.1** Date of completion of questionnaire: ☐☐/☐☐/☐☐☐☐

**1.2** Consultant responsible for case: _____

**1.3** Hospital name: _____

**1.4** Telephone number: _____ Email: _____

**1.5** Has the patient been referred from another centre? Yes: ☐ No: ☐ Not known: ☐

**If yes:** 1) please name centre: _____

_____

2) please name consultant: _____

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BPSU Study Questionnaire: Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

*This page of the case notification form will be stored separately from the rest of the questionnaire and personal identifying information for the case will be used only for linkage of records.*

## Section B: Case Details

**2.1** NHS/CHI Number: ☐☐☐ ☐☐☐ ☐☐☐☐

**2.2** Local Hospital Number: ☐☐☐☐☐☐☐☐☐☐

**2.3** Partial Postcode (first part only): ☐☐☐☐

**2.4** Sex: Male ☐ Female ☐

**2.5** Date of birth: DD/MM/YYYY

**2.6** Ethnicity:

**White**

Any White background ☐

**Mixed**

White and Black Caribbean ☐

White and Black African ☐

White and Asian ☐

Any Other Mixed background *(please specify below)* ☐

**Chinese or other ethnic group**

Chinese ☐

Any Other *(please specify below)* ☐

**Asian or British Asian**

Indian ☐

Pakistani ☐

Bangladeshi ☐

Any Other Asian background *(please specify below)* ☐

**Black or British Black**

Caribbean ☐

African ☐

Any Other Black background *(please specify below)* ☐

Please specify if any "Other" background: _____

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BPSU Study Questionnaire: Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

## Section C: Presentation & Initial Management

**3.1** Date of initial seizure: ☐☐/☐☐/☐☐☐☐

**3.2** Date of admission to hospital: ☐☐/☐☐/☐☐☐☐ Not admitted: ☐

**3.3** Did the patient have any subsequent seizures? Yes: ☐ No: ☐ Don't Know: ☐

**If yes**, How many? 1: ☐ 2: ☐ 3: ☐ 4: ☐ ≥ 5: ☐

**3.4** Please describe the nature of the seizure(s) (as witnessed or described in the history):

_____

_____

_____

_____

**3.5** Estimated duration of longest seizure: _____ minutes Not Known: ☐

**3.6** Was any treatment given to terminate the seizure(s)?: Yes: ☐ No: ☐ Don't know: ☐

**If yes**, what treatment was given:

Benzodiazepine (lorazepam / diazepam / midazolam) ☐ Phenytoin ☐

Phenobarbitone ☐ Paraldehyde ☐ Sedation and ventilation ☐

I.v. calcium gluconate ☐ I.v. calcium chloride ☐ I.v. / i.m. magnesium sulphate ☐

Any other treatment: *(please specify)* _____

_____

**3.7** Did the child have evidence of other clinical manifestations of vitamin D deficiency?

Clinically evident rickets (e.g. bowing of leg, ricketary rosary, craniotabes) ☐

Stunting of growth ☐

Fracture ☐

Cardiomyopathy ☐

Other: _____

_____

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BPSU Study Questionnaire: Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

## Section D: Investigations

Please indicate if any of the following tests were performed and their results: *(Please report values taken prior to initiation of treatment where available)*

**4.1** Serum calcium ($Ca^{2+}$):
Yes: **corrected** $Ca^{2+}$: ☐ No: ☐
Yes: **uncorrected** $Ca^{2+}$: ☐ Result pending: ☐
Result: _____ Units of measurement: _____
If only **uncorrected** calcium available, please also report the serum albumin: _____ g/L

**4.2** Serum 25-hydroxyvitamin D (25-OH-D):
Yes: ☐ No: ☐ Result pending: ☐
Result: _____ Units of measurement: _____

**4.3** Serum alkaline phosphatase (ALP):
Yes: ☐ No: ☐ Result pending: ☐
Result: _____ Units of measurement: _____

**4.4** Serum parathyroid hormone (PTH):
Yes: ☐ No: ☐ Result pending: ☐
Result: _____ Units of measurement: _____

**4.5** Serum phosphate:
Yes: ☐ No: ☐ Result pending: ☐
Result: _____ Units of measurement: _____

**4.6** X-ray of long bone (e.g. distal radius or femur):
Yes: ☐ No: ☐
**If yes**, were there any changes consistent with Rickets (i.e. cupping, widening, fraying of the metaphysis) ? Yes: ☐ No: ☐

**4.7** Electrocardiogram (ECG):
Yes: ☐ No: ☐
**If yes**, was there: A prolonged QT interval: Yes: ☐ No: ☐
Any other abnormalities: _____

**4.8** **Mother's** serum 25-hydroxy vitamin D (25-OH-D):
Yes: ☐ No: ☐ Result pending: ☐
Result: _____ Units of measurement: _____

## Section E: Maternal History

**5.1** If child < 2 years old, did the mother take vitamin D supplements (inlcuding multi-vitamin supplements containing vitamin D) at any time during pregnancy?
Yes: ☐ No: ☐ Don't know: ☐
**If yes**, which preparation and dose: _____ Don't know: ☐

**5.2** If the mother is currently breastfeeding her baby, is she taking any vitamin D supplements (including multi-vitamin supplements containing vitamin D)?
Yes: ☐ No: ☐ Not breastfeeding: ☐ Don't know: ☐
**If yes**, which preparation and dose: _____ Don't know: ☐

**5.3** Was the mother veiled / covered when you saw her? Yes: ☐ No: ☐ Don't know: ☐
**If yes**, was this: Full length / head-to-toe: ☐ Head scarf only: ☐

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BPSU Study Questionnaire: Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

## Section F: Medical & Nutritional History

**6.1** Does the child have any of the following medical conditions?

| | | | |
|---|---|---|---|
| Gastrointestinal disease with fat malabsorption | ☐ | Chronic renal disease | ☐ |
| Inherited disorder of vitamin D metabolism* | ☐ | Liver disease | ☐ |
| A condition necessitating total parenteral nutrition | ☐ | Epilepsy | ☐ |

**6.2** At the time of the seizure, did the child have any of the following medical conditions?

| | | | |
|---|---|---|---|
| Intracranial haemorrhage (e.g. IVH) | ☐ | Meningitis / encephalitis | ☐ |
| Hypoxic ischaemic encephalopathy (HIE) | ☐ | Cerebral infarction | ☐ |
| Hypo- or hypernatraemia (<125mmol/l or >155 mmol/l) | ☐ | Hypoglycaemia | ☐ |
| An inborn error of metabolism | ☐ | Drug withdrawal | ☐ |

**6.3** Does the child have any other medical condition(s)? Yes: ☐ No: ☐ Don't know: ☐

**If yes**, please specify: _____

_____

_____

**6.4** What was the child's gestational age at birth?

≥ 37 weeks: ☐ 32-36 weeks: ☐ 28 – 31 weeks: ☐ < 28 weeks: ☐ Don't Know: ☐

**6.5** Was the child on any medications at the time of admission? Yes: ☐ No: ☐ Not Known: ☐

**If yes**, please specify: *(including doses where known)* _____

_____

_____

**6.6** Feeding history. Is the child:

| | | | |
|---|---|---|---|
| Exclusively breast fed: | ☐ | Fed formula milk: | ☐ |
| Mixed breast / formula milk: | ☐ | Weaned onto solids: | ☐ |
| Don't Know: | ☐ | | |

**6.7** Does the child have any food allergies / intolerances? Yes: ☐ No: ☐ Don't know: ☐

**If yes**, please specify: _____

**6.8** If female, was the child veiled / covered when you saw her? Yes: ☐ No: ☐ Don't know: ☐

**If yes**, was this: Full length / head-to-toe ☐ Head scarf only ☐

* Inherited disorders of vitamin D metabolism include defects of 1-α hydroxylase, 25-α hydroxylase, and the vitamin D receptor (Vitamin D dependent rickets type 1 and 2)

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BPSU Study Questionnaire: Hypocalcaemic Seizures Secondary to Vitamin D Deficiency

## Section G: Outcome

**7.1** Has the child been discharged? Yes: ☐ **If yes**, date of discharge: DD/MM/YY

No: ☐

**If no**, what happened? Still admitted: ☐

Transferred: ☐ Name of hospital: _____

Name of consultant _____

Died: ☐ Date of death: DD/MM/YY

Was cause of death recorded? Yes: ☐ No: ☐

**If yes**, what: _____

**7.2** If discharged, were there any sequlae at discharge? Yes: ☐ No: ☐ Don't Know: ☐

**If yes**, specify: _____

_____

**7.3** Was the child discharged on any treatment? Yes: ☐ No: ☐ Don't Know: ☐

**If yes**, what was prescribed?

Vitamin D: ☐ **If yes**, which preparation? Colecalciferol ☐ Adcal D3 ☐

Calcichew D3 ☐ Abidec ☐

Dalivit ☐ Calcitriol ☐

Alfacalcidol ☐ Ergocalciferol ☐

Other preparation: _____

**Please specify the dose prescribed:** _____

Calcium supplement ☐ **If yes**, which preparation and dose: _____

Other medication: ☐ **If yes**, please specify: _____

_____

## Thank you for taking the time to complete the Questionnaire!

Please return the completed form in the postage-paid self-addressed envelope to:

Dr Emre Basatemur,
General & Adolescent Paediatric Unit, UCL Institute of Child Health, 30 Guilford Street, London, WC1N 1EH

Alternatively, email the completed form to: emre.basatemur@ucl.ac.uk

If you have any questions about the study please do not hesitate to contact Dr Emre Basatemur by email or telephone (0778 695 6113).

# Appendix E: Assessment for Interactions in Models Examining Rates of Diagnosis of Vitamin D Deficiency

E.1 Assessment for interaction between sex and ethnicity..... 303

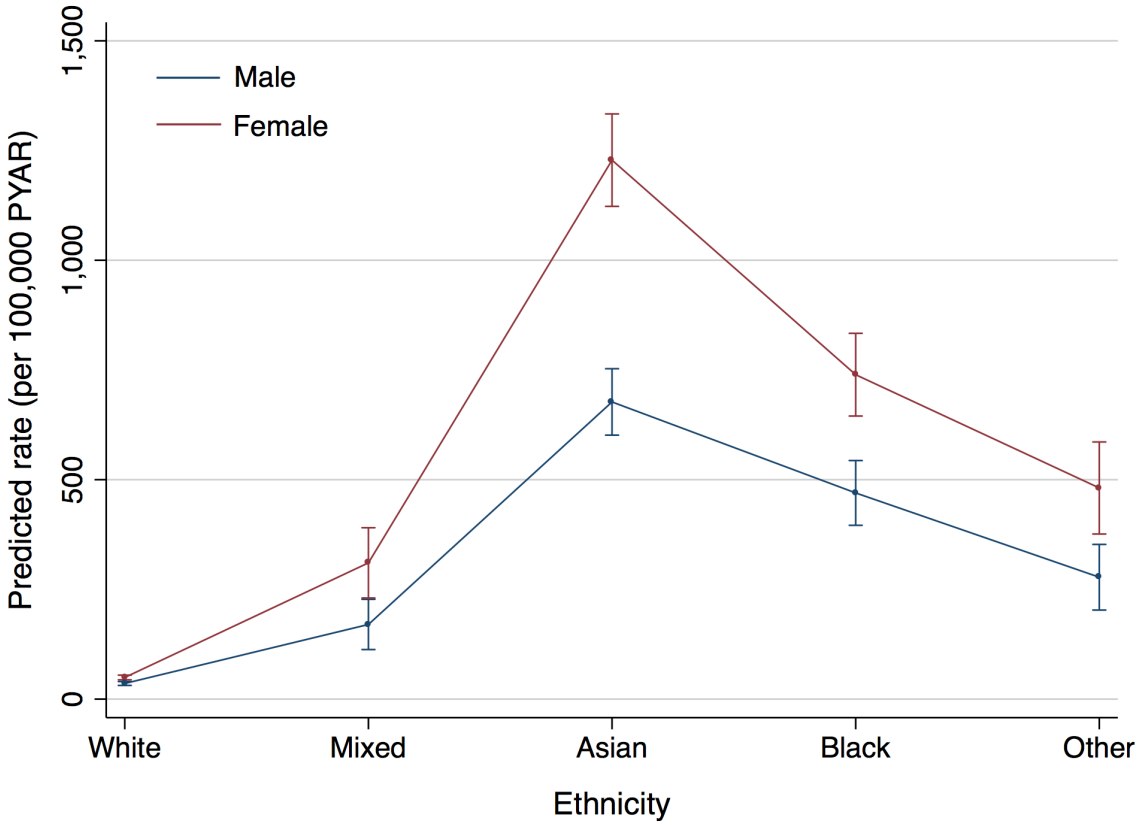
E.2 Assessment for interaction between age group and ethnicity..... 305

E.3 Assessment for interaction between ethnicity and Index of Multiple Deprivation..... 308

E.4 Assessment for interaction between sex and Index of Multiple Deprivation..... 311

E.5 Assessment for interaction between age group and Index of Multiple Deprivation..... 313

**Figure E.1** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of ethnicity, showing an interaction with sex.[a]




Abbreviations: PYAR, person-years at risk.

[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (age group, Index of Multiple Deprivation, and calendar year). The vertical bars represent 95% confidence intervals. Missing data was handled using complete cases analysis. n=414,182.

**Table E.1** Inclusion of an interaction term between sex and ethnicity, in the single-level Poisson regression model examining associations with the rate of diagnosis of vitamin D deficiency.

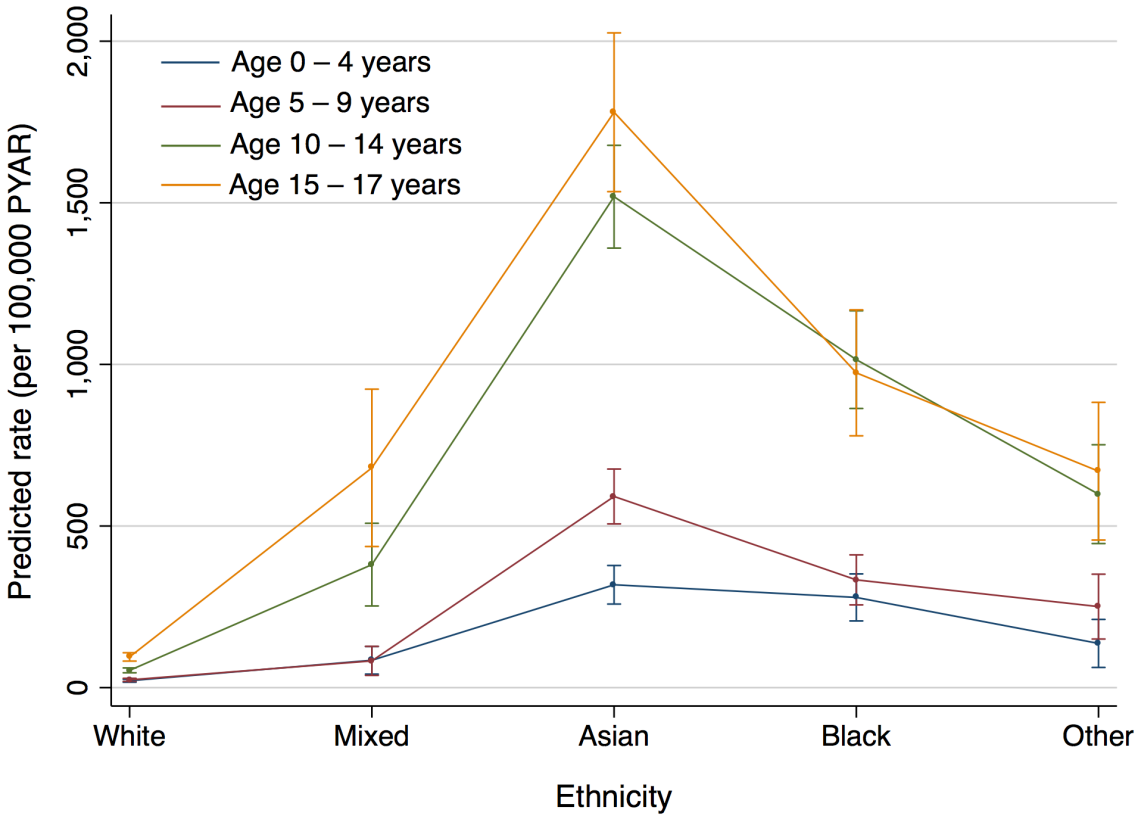
| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***Ethnicity*** | **Sex** | | |
| *White* | Male | Baseline | - |
| | Female | 1.39 (1.18–1.63) | <0.001 |
| *Asian or Asian British* | Male | Baseline | - |
| | Female | 1.81 (1.58–2.08) | <0.001 |
| *Black or black British* | Male | Baseline | - |
| | Female | 1.57 (1.29–1.92) | <0.001 |
| *Mixed* | Male | Baseline | - |
| | Female | 1.83 (1.20–2.79) | 0.005 |
| *Chinese or other* | Male | Baseline | - |
| | Female | 1.73 (1.23–2.45) | 0.002 |
| ***Sex*** | **Ethnicity** | | |
| *Male* | White | Baseline | - |
| | Asian or Asian British | 19.0 (16.1–22.5) | <0.001 |
| | Black or black British | 13.2 (10.8–16.1) | <0.001 |
| | Mixed | 4.78 (3.34–6.84) | <0.001 |
| | Chinese or other | 7.81 (5.80–10.5) | <0.001 |
| *Female* | White | Baseline | - |
| | Asian or Asian British | 24.9 (21.7–28.6) | <0.001 |
| | Black or black British | 15.0 (12.7–17.7) | <0.001 |
| | Mixed | 6.30 (4.76–8.33) | <0.001 |
| | Chinese or other | 9.76 (7.65–12.5) | <0.001 |

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Results from a single-level multivariable Poisson regression model, adjusted for the variables listed in the table in addition to age group, Index of Multiple Deprivation quintile, and calendar year. An interaction between sex and age group was included. Likelihood ratio test for interaction p-value 0.16. Missing data was handled using complete cases analysis. n=414,182.

[b] p-value for the null hypothesis that the true rate ratio is equal to 1.

**Figure E.2** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of ethnicity, showing an interaction with age group.[a]




Abbreviations: PYAR, person-years at risk.

[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (sex, Index of Multiple Deprivation, and calendar year). The vertical bars represent 95% confidence intervals. Missing data was handled using complete cases analysis. n=414,182.

**Table E.2** Inclusion of an interaction term between age group and ethnicity, in the single-level Poisson regression model examining associations with the rate of diagnosis of vitamin D deficiency.

| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***Ethnicity*** | **Age group** | | |
| *White* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.12 (0.84–1.51) | 0.435 |
| | 10 – 14 years | 2.51 (1.94–3.24) | <0.001 |
| | 15 – 17 years | 4.46 (3.46–5.75) | <0.001 |
| *Asian or Asian British* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.86 (1.47–2.35) | <0.001 |
| | 10 – 14 years | 4.77 (3.86–5.91) | <0.001 |
| | 15 – 17 years | 5.59 (4.44–7.06) | <0.001 |
| *Black or black British* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.19 (0.84–1.69) | 0.316 |
| | 10 – 14 years | 3.64 (2.70–4.90) | <0.001 |
| | 15 – 17 years | 3.49 (2.52–4.84) | <0.001 |
| *Mixed* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 0.98 (0.46–2.06) | 0.954 |
| | 10 – 14 years | 4.50 (2.45–8.26) | <0.001 |
| | 15 – 17 years | 8.04 (4.33–14.9) | <0.001 |
| *Chinese or other* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.83 (0.93–3.60) | 0.078 |
| | 10 – 14 years | 4.38 (2.40–7.98) | <0.001 |
| | 15 – 17 years | 4.90 (2.61–9.20) | <0.001 |
| ***Age Group*** | **Ethnicity** | | |
| *0 – 4 years* | White | Baseline | - |
| | Asian or Asian British | 14.9 (11.2–19.9) | <0.001 |
| | Black or black British | 13.1 (9.35–18.4) | <0.001 |
| | Mixed | 3.97 (2.29–6.88) | <0.001 |
| | Chinese or other | 6.42 (3.58–11.5) | <0.001 |
| *5 – 9 years* | White | Baseline | - |
| | Asian or Asian British | 24.7 (19.3–31.6) | <0.001 |
| | Black or black British | 13.9 (10.3–18.9) | <0.001 |
| | Mixed | 3.46 (1.94–6.17) | <0.001 |
| | Chinese or other | 10.5 (6.69–16.4) | <0.001 |
| *10 – 14 years* | White | Baseline | - |
| | Asian or Asian British | 28.5 (23.9–33.9) | <0.001 |
| | Black or black British | 19.0 (15.5–23.4) | <0.001 |
| | Mixed | 7.13 (4.95–10.3) | <0.001 |
| | Chinese or other | 11.2 (8.38–15.0) | <0.001 |

**Table E.2** Continued.

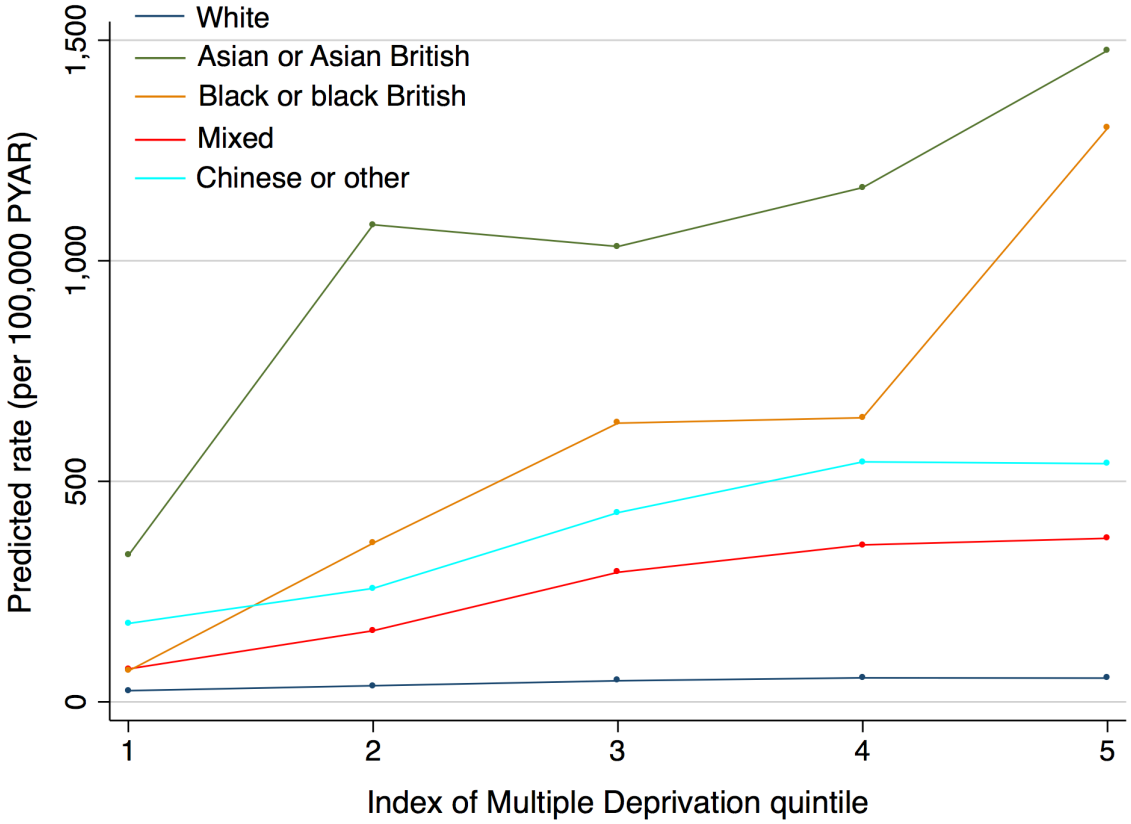
| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***Age Group*** | **Ethnicity** | | |
| *15 – 17 years* | White | Baseline | - |
| | Asian or Asian British | 18.7 (15.4–22.7) | <0.001 |
| | Black or black British | 10.3 (8.04–13.1) | <0.001 |
| | Mixed | 7.16 (4.88–10.5) | <0.001 |
| | Chinese or other | 7.05 (4.99–9.96) | <0.001 |

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Results from a single-level multivariable Poisson regression model, adjusted for the variables listed in the table in addition to sex, Index of Multiple Deprivation quintile, and calendar year. An interaction between age group and ethnicity was included. Likelihood ratio test for interaction p-value <0.001. Missing data was handled using complete cases analysis. n=414,182.

[b] p-value for the null hypothesis that the true rate ratio is equal to 1.

**Figure E.3** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of Index of Multiple Deprivation, showing an interaction with ethnicity.[a]




Abbreviations: PYAR, person-years at risk.

[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (sex, age group, and calendar year). Missing data was handled using complete cases analysis. n=414,182.

**Table E.3** Inclusion of an interaction term between ethnicity and Index of Multiple Deprivation, in the single-level Poisson regression model examining associations with the rate of diagnosis of vitamin D deficiency.

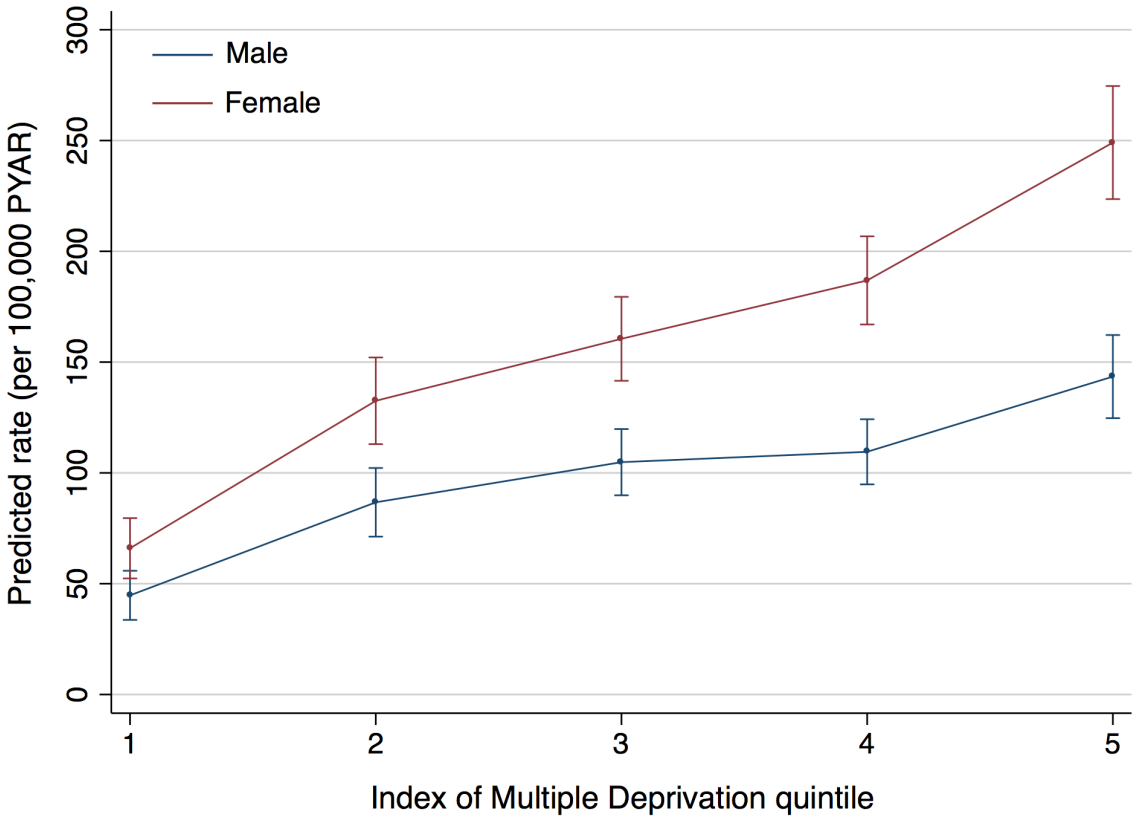
| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI)** [a] | **p-value** [b] |
|---|---|---|---|
| ***Ethnicity*** | **IMD quintile** | | |
| *White* | 1 (least deprived) | Baseline | - |
| | 2 | 1.45 (1.10–1.90) | 0.008 |
| | 3 | 1.89 (1.46–2.45) | <0.001 |
| | 4 | 2.15 (1.67–2.78) | <0.001 |
| | 5 (most deprived) | 2.13 (1.60–2.82) | <0.001 |
| *Asian or Asian British* | 1 (least deprived) | Baseline | - |
| | 2 | 3.26 (2.27–4.68) | <0.001 |
| | 3 | 3.10 (2.19–4.42) | <0.001 |
| | 4 | 3.51 (2.48–4.98) | <0.001 |
| | 5 (most deprived) | 4.45 (3.16–6.27) | <0.001 |
| *Black or black British* | 1 (least deprived) | Baseline | - |
| | 2 | 5.14 (1.55–17.1) | 0.008 |
| | 3 | 9.02 (2.85–28.6) | <0.001 |
| | 4 | 9.20 (2.92–28.9) | <0.001 |
| | 5 (most deprived) | 18.6 (5.93–58.1) | <0.001 |
| *Mixed* | 1 (least deprived) | Baseline | - |
| | 2 | 2.16 (0.75–6.21) | 0.154 |
| | 3 | 3.93 (1.48–10.4) | 0.006 |
| | 4 | 4.76 (1.85–12.3) | 0.001 |
| | 5 (most deprived) | 4.96 (1.89–13.0) | 0.001 |
| *Chinese or other* | 1 (least deprived) | Baseline | - |
| | 2 | 1.45 (0.66–3.15) | 0.352 |
| | 3 | 2.41 (1.23–4.72) | 0.010 |
| | 4 | 3.06 (1.59–5.90) | 0.001 |
| | 5 (most deprived) | 3.03 (1.48–6.23) | 0.002 |
| ***IMD quintile*** | **Ethnicity** | | |
| *1 (least deprived)* | White | Baseline | - |
| | Asian or Asian British | 13.1 (8.97–19.1) | <0.001 |
| | Black or black British | 2.76 (0.88–8.72) | 0.083 |
| | Mixed | 2.95 (1.20–7.24) | 0.018 |
| | Chinese or other | 7.01 (3.76–13.1) | <0.001 |
| *2* | White | Baseline | - |
| | Asian or Asian British | 29.5 (23.0–37.9) | <0.001 |
| | Black or black British | 9.82 (6.31–15.3) | <0.001 |
| | Mixed | 4.40 (2.37–8.18) | <0.001 |
| | Chinese or other | 7.02 (4.09–12.0) | <0.001 |

**Table E.3** Continued.

| *Stratifying variable* | Effect of covariate | RR for diagnosis of vitamin D deficiency (95% CI) [a] | p-value [b] |
|---|---|---|---|
| ***IMD quintile*** | **Ethnicity** | | |
| *3* | White | Baseline | - |
| | Asian or Asian British | 21.6 (17.3–26.9) | <0.001 |
| | Black or black British | 13.2 (9.96–17.5) | <0.001 |
| | Mixed | 6.13 (3.91–9.63) | <0.001 |
| | Chinese or other | 8.96 (6.25–12.8) | <0.001 |
| *4* | White | Baseline | - |
| | Asian or Asian British | 21.4 (17.3–26.4) | <0.001 |
| | Black or black British | 11.8 (9.27–15.0) | <0.001 |
| | Mixed | 6.52 (4.40–9.66) | <0.001 |
| | Chinese or other | 9.97 (7.17–13.9) | <0.001 |
| *5 (most deprived)* | White | Baseline | - |
| | Asian or Asian British | 27.4 (21.7–34.6) | <0.001 |
| | Black or black British | 24.1 (18.8–31.0) | <0.001 |
| | Mixed | 6.88 (4.39–10.8) | <0.001 |
| | Chinese or other | 10.0 (6.35–15.8) | <0.001 |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results from a single-level multivariable Poisson regression model, adjusted for the variables listed in the table in addition to sex, age group, and calendar year. An interaction between ethnicity and Index of Multiple Deprivation was included. Likelihood ratio test for interaction p-value <0.001. Missing data was handled using complete cases analysis. n=414,182.
[b] p-value for the null hypothesis that the true rate ratio is equal to 1.

**Figure E.4** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of Index of Multiple Deprivation, showing an interaction with sex.[a]




Abbreviations: PYAR, person-years at risk.

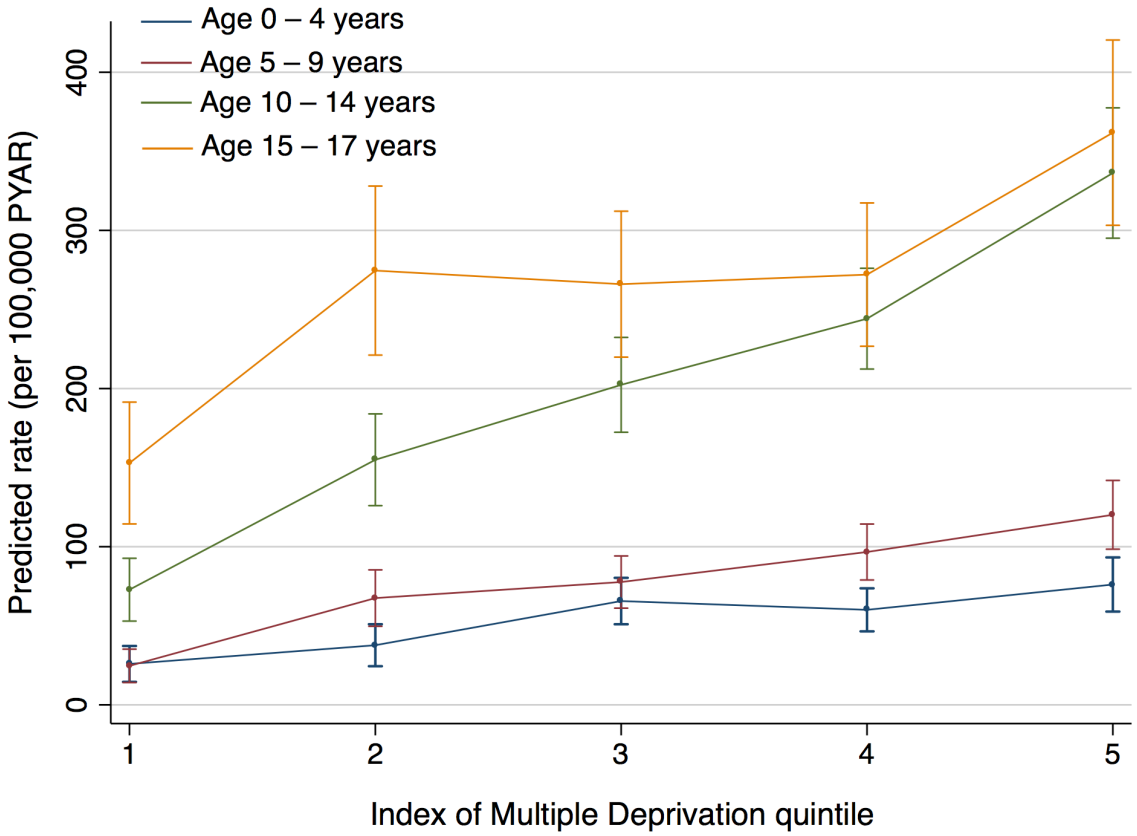
[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (age group, ethnicity, and calendar year). The vertical bars represent 95% confidence intervals. Missing data was handled using complete cases analysis. n=414,182.

**Table E.4** Inclusion of an interaction term between sex and Index of Multiple Deprivation, in the single-level Poisson regression model examining associations with the rate of diagnosis of vitamin D deficiency.

| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***IMD Quintile*** | **Sex** | | |
| *1 (least deprived)* | Male | Baseline | - |
| | Female | 1.47 (1.07–2.03) | 0.018 |
| *2* | Male | Baseline | - |
| | Female | 1.53 (1.21–1.93) | <0.001 |
| *3* | Male | Baseline | - |
| | Female | 1.53 (1.27–1.84) | <0.001 |
| *4* | Male | Baseline | - |
| | Female | 1.71 (1.44–2.02) | <0.001 |
| *5 (most deprived)* | Male | Baseline | - |
| | Female | 1.74 (1.47–2.05) | <0.001 |
| ***Sex*** | **IMD Quintile** | | |
| *Male* | 1 (least deprived) | Baseline | - |
| | 2 | 1.94 (1.43–2.63) | <0.001 |
| | 3 | 2.34 (1.76–3.12) | <0.001 |
| | 4 | 2.45 (1.85–3.25) | <0.001 |
| | 5 (most deprived) | 3.21 (2.42–4.25) | <0.001 |
| *Female* | 1 (least deprived) | Baseline | - |
| | 2 | 2.01 (1.56–2.59) | <0.001 |
| | 3 | 2.43 (1.92–3.09) | <0.001 |
| | 4 | 2.83 (2.24–3.57) | <0.001 |
| | 5 (most deprived) | 3.78 (3.00–4.76) | <0.001 |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results from a single-level multivariable Poisson regression model, adjusted for the variables listed in the table in addition to age group, ethnicity, and calendar year. An interaction between sex and Index of Multiple Deprivation was included. Likelihood ratio test for interaction p-value 0.75. Missing data was handled using complete cases analysis. n=414,182.
[b] p-value for the null hypothesis that the true rate ratio is equal to 1.

**Figure E.5** Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of Index of Multiple Deprivation, showing an interaction with age group.[a]




Abbreviations: PYAR, person-years at risk.

[a] Predicted margins were derived from a single-level multivariable Poisson regression model, at average values for the remaining covariates (sex, ethnicity, and calendar year). The vertical bars represent 95% confidence intervals. Missing data was handled using complete cases analysis. n=414,182.

**Table E.5** Inclusion of an interaction term between age group and Index of Multiple Deprivation, in the single-level Poisson regression model examining associations with the rate of diagnosis of vitamin D deficiency.

| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***IMD quintile*** | **Age group** | | |
| *1 (least deprived)* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 0.95 (0.52–1.76) | 0.877 |
| | 10 – 14 years | 2.81 (1.68–4.71) | <0.001 |
| | 15 – 17 years | 5.91 (3.57–9.80) | <0.001 |
| *2* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.79 (1.15–2.78) | 0.009 |
| | 10 – 14 years | 4.11 (2.76–6.12) | <0.001 |
| | 15 – 17 years | 7.28 (4.87–10.9) | <0.001 |
| *3* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.18 (0.87–1.61) | 0.286 |
| | 10 – 14 years | 3.08 (2.36–4.03) | <0.001 |
| | 15 – 17 years | 4.05 (3.05–5.38) | <0.001 |
| *4* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.61 (1.20–2.15) | 0.001 |
| | 10 – 14 years | 4.06 (3.13–5.28) | <0.001 |
| | 15 – 17 years | 4.53 (3.42–6.00) | <0.001 |
| *5 (most deprived)* | 0 – 4 years | Baseline | - |
| | 5 – 9 years | 1.58 (1.18–2.11) | 0.002 |
| | 10 – 14 years | 4.42 (3.42–5.71) | <0.001 |
| | 15 – 17 years | 4.76 (3.60–6.27) | <0.001 |
| ***Age Group*** | **IMD quintile** | | |
| *0 – 4 years* | 1 (least deprived) | Baseline | - |
| | 2 | 1.46 (0.83–2.56) | 0.189 |
| | 3 | 2.54 (1.55–4.15) | <0.001 |
| | 4 | 2.32 (1.42–3.81) | 0.001 |
| | 5 (most deprived) | 2.94 (1.80–4.82) | <0.001 |
| *5 – 9 years* | 1 (least deprived) | Baseline | - |
| | 2 | 2.74 (1.66–4.53) | <0.001 |
| | 3 | 3.15 (1.95–5.08) | <0.001 |
| | 4 | 3.92 (2.46–6.25) | <0.001 |
| | 5 (most deprived) | 4.87 (3.06–7.76) | <0.001 |
| *10 – 14 years* | 1 (least deprived) | Baseline | - |
| | 2 | 2.13 (1.53–2.96) | <0.001 |
| | 3 | 2.78 (2.04–3.79) | <0.001 |
| | 4 | 3.35 (2.48–4.54) | <0.001 |
| | 5 (most deprived) | 4.62 (3.42–6.23) | <0.001 |

**Table E.2** Continued.

| ***Stratifying variable*** | **Effect of covariate** | **RR for diagnosis of vitamin D deficiency (95% CI) [a]** | **p-value [b]** |
|---|---|---|---|
| ***Age Group*** | **IMD quintile** | | |
| *15 – 17 years* | 1 (least deprived) | Baseline | - |
| | 2 | 1.80 (1.31–2.47) | <0.001 |
| | 3 | 1.74 (1.28–2.36) | <0.001 |
| | 4 | 1.78 (1.32–2.41) | <0.001 |
| | 5 (most deprived) | 2.37 (1.75–3.19) | <0.001 |

Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; RR, rate ratio.
[a] Results from a single-level multivariable Poisson regression model, adjusted for the variables listed in the table in addition to sex, ethnicity, and calendar year. An interaction between age group and Index of Multiple Deprivation was included. Likelihood ratio test for interaction p-value 0.016. Missing data was handled using complete cases analysis. n=414,182.
[b] p-value for the null hypothesis that the true rate ratio is equal to 1.

# Appendix F: Proximity Rules for Child to Mother Linkage

F.1 Proximity rules for child to mother linkage using pregnancy or delivery related AHD codes ……..... 317

F.2 Proximity rules for child to mother linkage using pregnancy or delivery related Read codes groups …….. 319

**Table F.1** Proximity rules for child to mother linkage using pregnancy or delivery related AHD codes.

| AHD code | Description | Proximity rule for children with month of birth (MOB) available [b] | Proximity rule for children with only year of birth (YOB) available [c] |
|---|---|---|---|
| 1001400092 | Pregnancy test [d] | - Record date 0-9 months before MOB | - None [e] |
| 1001400161 | Maternity ultra sound scan | - EDD 4 months before to 2 months after MOB<br>- If EDD not available, record date 0-8 months before MOB | - EDD in same year as YOB<br>- If EDD not available and record date between Jan to June, if record in same year as YOB<br>- If EDD not available and record date between July to Dec, if record in previous year to YOB. |
| 1001400306 | Ante natal blood tests | - Record date 0-9 months before MOB | - If record date between Jan to July and in same year as YOB.<br>- If record date between Aug to Dec and in previous year to YOB |
| 1009800000 | CHS – APGAR Score At 1 Minute | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1009810000 | CHS – APGAR Score At 5 Minutes | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1015000000 | Maternity outcome [f] | - Delivery date 0-2 months 0-2 months after MOB<br>- If delivery date not available, record date 0-2 months after MOB | - Delivery date in same year as YOB<br>- If delivery date not available, record in same year as YOB |
| 1040000000 | Ante natal booking | - EDD 1 month before to 2 months after MOB<br>- If EDD not available, record date 0-9 months before MOB | - EDD in same year as YOB<br>- If EDD not available and record date between Jan to June, if record in same year as YOB<br>- If EDD not available and record date between July to Dec, if record in previous year to YOB. |
| 1041000000 | Ante natal consultation | - EDD 1 month before to 2 months after MOB<br>- If EDD not available, record date 0-8 months before MOB | - EDD in same year as YOB<br>- No match if EDD not available [e] |
| 1044000000 | Postnatal examination | - Delivery date 1 month before to 2 months after MOB<br>- If delivery date not available, record date 0-4 months after MOB | - Delivery date in same year as YOB<br>- If delivery date not available and record date between Jan to Feb, if record in previous year to YOB<br>- If delivery date not available and record date between March to Dec, if record in same year as YOB |
| 1044100000 | Postnatal visit | - Delivery date 1 month before to 1 month after MOB<br>- If delivery date not available, record date 0-2 months after MOB | - Delivery date in same year as YOB<br>- If delivery date not available, record in same year as YOB |
| 1046100000 | Ante natal fetal examination | - Record date 0-8 months before MOB | - If record date between Jan to Oct and in same year as YOB<br>- If record date between Nov to Dec and in previous year to YOB |
| 1047000000 | Maternity outcome gestational age of baby | - Record date 1 month before to 2 months after MOB | - Record in same year as YOB |

**Table F.1** Continued.

| AHD code | Description | - **Proximity rule for children with month of birth (MOB) available** [b] | - **Proximity rule for children with only year of birth (YOB) available** [c] |
|---|---|---|---|
| 1048000000 | Maternity pregnancy dates – event date = LMP date | - EDD 1 month before to 1 month after MOB | - EDD in same year as YOB |
| 1048100000 | Maternity delivery details baby [f] | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1048200000 | Maternity placenta | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1049000000 | CHS – gestation | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1050300000 | Maternity feeding | - Record date 0-3 months after MOB | - Record in same year as YOB |
| 1052500000 | Maternity infant details [f] | - Record date 0-3 months after MOB | - Record in same year as YOB |
| 1055400000 | Maternity perineum | - Record date 0-2 months after MOB | - Record in same year as YOB |
| 1055405000 | Maternity care plan | - Record date 0-9 months before MOB | - If record date between Jan to June and in same year as YOB<br>- If record date between July to Dec and in previous year to YOB |
| 1055500000 | CHS – delivery details [f] | - Record date 0-1 months after MOB | - Record in same year as YOB |
| 1055520000 | Maternity stages of labour | - Record date 0-2 months after MOB | - Record in same year as YOB |

Abbreviations: AHD, additional health data; EDD, estimated date of delivery; MOB, month of birth; YOB, year of birth.

[a] Where the AHD code provides information regarding the EDD or actual delivery date, the proximity rule refers to the difference in time between the child's month or year of birth and the EDD or actual delivery date. Where information regarding the EDD or actual delivery date is not recorded, the proximity rule refers to the difference in time between the child's month or year of birth and the AHD code record date. The proximity rules were applied where women who had a pregnancy or delivery related AHD code in their medical record were registered with the same general practice as a child in the study cohort with overlapping periods of active registration, shared an identical 'household' identifier with the child, and were between 14 to 50 older than the child.

[b] Month of birth was available for children below 15 years of age at February 2015.

[c] Year of birth only was available for children 15 years of age or older at February 2015.

[d] Only included in linkage if the test was specified as being positive.

[e] The distribution of timing of records in relation to children's birth was considered to be too wide to allow reliable matching of records when only the year of birth was available for children.

[f] Not included in linkage if the outcome was specified as being a stillbirth, miscarriage, or neonatal death.

**Table F.2** Proximity rules for child to mother linkage using pregnancy or delivery related Read code groups.

| Read code group | Proximity rule for children with month of birth (MOB) available [b] | Proximity rule for children with only year of birth (YOB) available [c] |
|---|---|---|
| Pregnant | - Record date 0-9 months before MOB | - If record date between Jan to May and in same year as YOB<br>- If record date between June to Dec and in previous year to YOB |
| Pregnancy Test | - Record date 5-9 months before MOB | - If record date between Jan to April and in same year as YOB<br>- If record date between May to Dec and in previous year to YOB |
| Antenatal ultrasound scan | - Record date 1-8 months before MOB | - If record date between Jan to May and in same year as YOB.<br>- If record date between June to Dec and in previous year to YOB |
| Antenatal examination | - Record date 0-8 months before MOB | - If record date between Jan to Nov and in same year as YOB.<br>- If record date in Dec and in previous year to YOB |
| Antenatal care | - Record date 0-9 months before MOB | - If record date between Jan to June and in same year as YOB.<br>- If record date between July to Dec and in previous year to YOB |
| Antenatal screening or test | - Record date 0-8 months before MOB | - If record date between Jan to July and in same year as YOB.<br>- If record date between August to Dec and in previous year to YOB |
| Delivery booking | - Record date 0-8 months before MOB | - If record date between Jan to June and in same year as YOB.<br>- If record date between July to Dec and in previous year to YOB |
| Estimated delivery date | - Record date 9 months before to 1 month after MOB | - If record date between Jan to July and in same year as YOB.<br>- If record date between August to Dec and in previous year to YOB |
| Amniocentesis | - Record date 3-7 months before MOB | - If record date between Jan to July and in same year as YOB.<br>- If record date between August to Dec and in previous year to YOB |
| Birth or delivery | - Record date 0-2 months after MOB | - Record in same year as YOB |
| Length of labour | - Record date in same month as MOB | - Record in same year as YOB |
| Mode of birth | - Record date 0-1 months after MOB | - Record in same year as YOB |
| Sex of baby | - Record date 0-1 months after MOB | - Record in same year as YOB |
| Gestational age | - Record date in same month as MOB | - Record in same year as YOB |
| Postnatal visit | - Record date 0-1 months after MOB | - Record in same year as YOB |
| Postnatal care | - Record date 0-1 months after MOB | - Record in same year as YOB |
| Postnatal examination | - Record date 0-3 months after MOB | - If record date between Jan to Feb and in subsequent year to YOB.<br>- If record date between March to Dec and in the same year to YOB |
| Hearing screen | - Record date in same month as MOB | - Record in same year as YOB |
| Newborn registration | - Record date 0-1 months after MOB | - Record in same year as YOB |

Abbreviations: MOB, month of birth; YOB, year of birth.

[a] The proximity rule refers to the difference in time between the child's month or year of birth and the Read code record date. The proximity rules were applied where women who had a pregnancy or delivery related Read code (see appendix G.3) in their medical record were registered with the same general practice as a child in the study cohort with overlapping periods of active registration, shared an identical 'household' identifier with the child, and were between 14 to 50 older than the child.

[b] Month of birth was available for children below 15 years of age at February 2015.

[c] Year of birth only was available for children 15 years of age or older at February 2015.

## Appendix G: Code Lists

G.1 Drug Codes Referring to Pure Preparations of Calciferol ..... 321

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G.4 Read codes related to liver disease ..... 352

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G.6 Read codes related to conditions associated with gastrointestinal malabsorption ..... 366

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**Table G.9** Drug codes referring to pure preparations of calciferol.

| Drug code | Code description | Dosage unit | IU of calciferol per dosage unit |
|---|---|---|---|
| 52073979 | Colecalciferol 40,000unit capsules | tablet / cap | 40000 |
| 52074979 | Colecalciferol 40,000unit capsules | tablet / cap | 40000 |
| 52154979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 53089979 | Colecalciferol 15,000units/5ml oral solution | ml | 3000 |
| 53090979 | Colecalciferol 15,000units/5ml oral solution | ml | 3000 |
| 53091979 | Colecalciferol 15,000units/5ml oral solution | ml | 3000 |
| 53092979 | Colecalciferol 15,000units/5ml oral solution | ml | 3000 |
| 53322979 | Ergocalciferol 125microgram tablets | tablet / cap | 5000 |
| 53356979 | Colecalciferol 30,000unit capsules | tablet / cap | 30000 |
| 53357979 | Colecalciferol 5,000unit capsules | tablet / cap | 5000 |
| 53359979 | Ergocalciferol 12.5microgram tablets | tablet / cap | 500 |
| 53362979 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 53365979 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 53366979 | Colecalciferol 600unit capsules | tablet / cap | 600 |
| 53367979 | Colecalciferol 2,200unit capsules | tablet / cap | 2200 |
| 53368979 | Colecalciferol 10,000unit capsules | tablet / cap | 10000 |
| 53370979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 53371979 | Colecalciferol 50,000unit capsules | tablet / cap | 50000 |
| 53641979 | Ergocalciferol 250microgram tablets | tablet / cap | 10000 |
| 53650979 | Ergocalciferol 1.25mg capsules | tablet / cap | 50000 |
| 54637979 | Colecalciferol 500unit capsules | tablet / cap | 500 |
| 54638979 | Colecalciferol 500unit capsules | tablet / cap | 500 |
| 54716979 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 54889979 | Colecalciferol 3,000units/ml oral solution | ml | 3000 |
| 54890979 | Colecalciferol 2,000units/ml oral solution | ml | 2000 |
| 54891979 | Colecalciferol 2,000units/ml oral solution | ml | 2000 |
| 54916979 | COLECALCIFEROL 800iu tablets | tablet / cap | 800 |
| 54917979 | Colecalciferol 800unit tablets | tablet / cap | 800 |
| 55053979 | Colecalciferol 3,000unit tablets | tablet / cap | 3000 |
| 55054979 | Colecalciferol 20,000unit tablets | tablet / cap | 20000 |
| 55055979 | Colecalciferol 2,200unit tablets | tablet / cap | 2200 |
| 55056979 | Colecalciferol 10,000unit tablets | tablet / cap | 10000 |
| 55060979 | Colecalciferol 5,000unit tablets | tablet / cap | 5000 |
| 55061979 | Ergocalciferol 3,000units/ml oral solution | ml | 3000 |
| 55062979 | Ergocalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 55064979 | Colecalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 55065979 | Colecalciferol 20,000units/ml oral solution sugar free | ml | 20000 |
| 55066979 | Colecalciferol 30,000unit capsules | tablet / cap | 30000 |
| 55067979 | Colecalciferol 30,000unit capsules | tablet / cap | 30000 |
| 55068979 | Colecalciferol 5,000unit capsules | tablet / cap | 5000 |
| 55070979 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 55072979 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 55074979 | Colecalciferol 2,200unit capsules | tablet / cap | 2200 |
| 55076979 | Colecalciferol 10,000unit capsules | tablet / cap | 10000 |
| 55077979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 55078979 | Colecalciferol 50,000unit capsules | tablet / cap | 50000 |
| 55079979 | Colecalciferol 50,000unit capsules | tablet / cap | 50000 |
| 55558979 | Ergocalciferol 50,000unit capsules | tablet / cap | 50000 |
| 56123979 | Ergocalciferol 1.25mg capsules | tablet / cap | 50000 |
| 56242979 | Colecalciferol 3,000unit tablets | tablet / cap | 3000 |
| 56244979 | Colecalciferol 20,000unit tablets | tablet / cap | 20000 |
| 56246979 | Colecalciferol 2,200unit tablets | tablet / cap | 2200 |
| 56248979 | Colecalciferol 10,000unit tablets | tablet / cap | 10000 |
| 56310979 | Colecalciferol 400unit tablets | tablet / cap | 400 |
| 56313979 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 57965979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 58139979 | Colecalciferol 5,000unit tablets | tablet / cap | 5000 |
| 58209979 | Ergocalciferol 3,000units/ml oral solution | ml | 3000 |
| 58346979 | Colecalciferol 800unit capsules | tablet / cap | 800 |
| 58349979 | Colecalciferol 5,000unit capsules | tablet / cap | 5000 |
| 58353979 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 58355979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 58356979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |

**Table G.1** Continued.

| Drug code | Code description | Dosage unit | IU of calciferol per dosage unit |
|---|---|---|---|
| 58768979 | Colecalciferol 2,000units/ml oral solution sugar free | ml | 2000 |
| 58769979 | Colecalciferol 2,000units/ml oral solution sugar free | ml | 2000 |
| 58782979 | Colecalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 59769979 | Colecalciferol 800units/ml oral drops sugar free | ml | 800 |
| 59770979 | Colecalciferol 800units/ml oral drops sugar free | ml | 800 |
| 59771979 | Colecalciferol 400units/dose oral spray sugar free | spray | 400 |
| 59772979 | Colecalciferol 400units/dose oral spray sugar free | spray | 400 |
| 59843979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 59981979 | Ergocalciferol 15,000units/5ml oral solution | ml | 3000 |
| 60056979 | Ergocalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 60225979 | Colecalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 60568979 | Ergocalciferol 20,000units/ml oral solution sugar free | ml | 20000 |
| 60572979 | Colecalciferol 20,000units/ml oral solution sugar free | ml | 20000 |
| 60594979 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 61563979 | Colecalciferol 30,000units/5ml oral solution | ml | 6000 |
| 61592979 | Colecalciferol 2,000units/ml oral drops sugar free | ml | 2000 |
| 61593979 | Colecalciferol 2,000units/ml oral drops sugar free | ml | 2000 |
| 61910979 | Colecalciferol 400unit tablets | tablet / cap | 400 |
| 61911979 | Colecalciferol 400unit tablets | tablet / cap | 400 |
| 62001979 | Colecalciferol 1,000units/ml oral solution | ml | 1000 |
| 62002979 | Colecalciferol 1,000units/ml oral solution | ml | 1000 |
| 62088979 | Colecalciferol 10,000units/ml oral solution | ml | 10000 |
| 62116979 | Colecalciferol 5,000unit capsules | tablet / cap | 5000 |
| 62118979 | Colecalciferol 3,000unit capsules | tablet / cap | 3000 |
| 62152979 | Colecalciferol 6,000units/5ml oral suspension | ml | 1200 |
| 62324979 | Colecalciferol 20,000units/ml oral drops | ml | 20000 |
| 62356979 | Ergocalciferol 12.5microgram tablets | tablet / cap | 500 |
| 62357979 | Ergocalciferol 12.5microgram tablets | tablet / cap | 500 |
| 62536979 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 62622979 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 62626979 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 62643979 | Colecalciferol 600unit capsules | tablet / cap | 600 |
| 62645979 | Colecalciferol 2,200unit capsules | tablet / cap | 2200 |
| 62986979 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 63201979 | Colecalciferol 2,000unit capsules | tablet / cap | 2000 |
| 68364979 | Ergocalciferol 400units/5ml oral solution | ml | 80 |
| 68382979 | Ergocalciferol 20,000units/5ml oral suspension | ml | 4000 |
| 68384979 | Ergocalciferol 20,000units/5ml oral solution | ml | 4000 |
| 68392979 | Ergocalciferol 120units/5ml oral solution | ml | 24 |
| 68396979 | Ergocalciferol 100,000units/5ml oral solution | ml | 20000 |
| 78390978 | Colecalciferol 2,000unit orodispersible tablets sugar free | tablet / cap | 2000 |
| 78426978 | Colecalciferol 2,200unit tablets | tablet / cap | 2200 |
| 78428978 | Colecalciferol 5,000unit tablets | tablet / cap | 5000 |
| 78719978 | Colecalciferol 2,000unit tablets | tablet / cap | 2000 |
| 78720978 | Colecalciferol 2,000unit tablets | tablet / cap | 2000 |
| 79322978 | Colecalciferol 200units/drop oral drops sugar free | drops | 200 |
| 79338978 | Ergocalciferol 6,000units/5ml oral solution | ml | 1200 |
| 79960978 | Colecalciferol 280unit chewable tablets | tablet / cap | 280 |
| 79961978 | Colecalciferol 280unit chewable tablets | tablet / cap | 280 |
| 79993978 | Colecalciferol 20,000unit tablets | tablet / cap | 20000 |
| 80016978 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 80022978 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 80153979 | Ergocalciferol 50,000units/5ml oral suspension | ml | 10000 |
| 80157979 | Ergocalciferol 30,000units/5ml oral suspension | ml | 6000 |
| 80169979 | Ergocalciferol 10,000units/5ml oral suspension | ml | 2000 |
| 80416979 | Colecalciferol 15,000units/5ml oral suspension | ml | 3000 |
| 80883998 | Colecalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 80885998 | Colecalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 80886998 | Colecalciferol 20,000units/ml oral solution sugar free | ml | 20000 |
| 80887998 | Colecalciferol 20,000units/ml oral solution sugar free | ml | 20000 |
| 80914998 | Colecalciferol 2,000units/ml oral drops sugar free | ml | 2000 |
| 80915998 | Colecalciferol 2,000units/ml oral drops sugar free | ml | 2000 |
| 80947998 | Ergocalciferol 20,000units/ml oral solution sugar free | ml | 20000 |

**Table G.1** Continued.

| Drug code | Code description | Dosage unit | IU of calciferol per dosage unit |
|---|---|---|---|
| 80952998 | COLECALCIFEROL 800iu capsules | tablet / cap | 800 |
| 80958998 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 81004998 | Colecalciferol 30,000unit capsules | tablet / cap | 30000 |
| 81007998 | Colecalciferol 30,000unit capsules | tablet / cap | 30000 |
| 81009998 | Colecalciferol 10,000unit capsules | tablet / cap | 10000 |
| 81010998 | Colecalciferol 10,000unit capsules | tablet / cap | 10000 |
| 81011998 | Colecalciferol 2,500unit capsules | tablet / cap | 2500 |
| 81012998 | Colecalciferol 2,500unit capsules | tablet / cap | 2500 |
| 81013998 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 81014998 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 81015998 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 81074998 | Colecalciferol 5,000unit capsules | tablet / cap | 5000 |
| 81138998 | Colecalciferol 500 units tablets | tablet / cap | 500 |
| 81252998 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 81253998 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 81328998 | Colecalciferol 800unit capsules | tablet / cap | 800 |
| 81329998 | Colecalciferol 800unit capsules | tablet / cap | 800 |
| 81335998 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 81464998 | Colecalciferol 400unit capsules | tablet / cap | 400 |
| 81568998 | Colecalciferol 10000units/ml oral solution | ml | 10000 |
| 81612998 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 81624998 | Colecalciferol 10,000units/5ml oral suspension | ml | 2000 |
| 81631998 | Colecalciferol 2,200unit capsules | tablet / cap | 2200 |
| 81710998 | Colecalciferol 50,000unit capsules | tablet / cap | 50000 |
| 82283998 | Colecalciferol 15,000units/5ml oral solution | ml | 3000 |
| 82513998 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 82514998 | Ergocalciferol 1.25mg capsules | tablet / cap | 50000 |
| 82946978 | Colecalciferol 20,000unit tablets | tablet / cap | 20000 |
| 82956978 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 83393978 | Colecalciferol 50,000unit tablets | tablet / cap | 50000 |
| 83468978 | COLECALCIFEROL 20,000iu tabs | tablet / cap | 20000 |
| 83744978 | Colecalciferol 5,000units/5ml oral solution | ml | 1000 |
| 83746978 | Colecalciferol 5,000units/5ml oral solution | ml | 1000 |
| 83747978 | Colecalciferol 10,000units/5ml oral solution | ml | 2000 |
| 83748978 | Colecalciferol 10,000units/5ml oral solution | ml | 2000 |
| 83750978 | Colecalciferol 10,000units/5ml oral solution | ml | 2000 |
| 84072978 | Colecalciferol 5,000unit tablets | tablet / cap | 5000 |
| 84414978 | Ergocalciferol 1,500units/ml oral solution sugar free | ml | 1500 |
| 84586978 | Colecalciferol 20,000unit tablets | tablet / cap | 20000 |
| 84592978 | Colecalciferol 400unit tablets | tablet / cap | 400 |
| 84600978 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 84680998 | Colecalciferol oral liquid | ml | - |
| 85005998 | Ergocalciferol oral liquid | ml | - |
| 85220998 | Ergocalciferol 600,000units/2ml solution for injection ampoules | ml | 300000 |
| 85224998 | Ergocalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 86614979 | Ergocalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 86615979 | Ergocalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 93163990 | Ergocalciferol 600,000units/2ml solution for injection ampoules | ml | 300000 |
| 93164990 | Ergocalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 93384992 | CALCIFEROL 10 MCG TAB | tablet / cap | 400 |
| 93390992 | CALCIFEROL 1,000 IU I/U TAB | tablet / cap | 1000 |
| 93401992 | CALCIFEROL 5000 I/U TAB | tablet / cap | 5000 |
| 94809990 | Ergocalciferol 1.25mg tablets | tablet / cap | 50000 |
| 94810990 | Ergocalciferol 250microgram tablets | tablet / cap | 10000 |
| 95606992 | ERGOCALCIF 600ku/1.5mL soln | ml | 400000 |
| 95872992 | CALCIFEROL 3,000 IU TAB | tablet / cap | 3000 |
| 95873992 | CALCIFEROL 30,000 IU/ML INJ | ml | 30000 |
| 95875992 | CALCIFEROL SOLN 400U/5ML IN ARACHIS OIL SOL | ml | 80 |
| 95877992 | CALCIFEROL 40,000 IU/ML INJ | ml | 40000 |
| 95878992 | CALCIFEROL 400 IU/ML SOL | ml | 400 |
| 96131992 | CALCIFEROL 400 IU/ML I/U SYR | ml | 400 |
| 96132992 | CALCIFEROL .25 MG CAP | tablet / cap | 10000 |
| 96133992 | CALCIFEROL 1 MG CAP | tablet / cap | 40000 |

**Table G.1** Continued.

| Drug code | Code description | Dosage unit | IU of calciferol per dosage unit |
|---|---|---|---|
| 96134992 | CALCIFEROL 1,000 IU I/U CAP | tablet / cap | 1000 |
| 96599992 | CALCIFEROL 75 MCG INJ | - | 3000 |
| 96600992 | CALCIFEROL STRONG MG TAB | tablet / cap | 10000 |
| 96601992 | CALCIFEROL 20,000 IU CAP | tablet / cap | 20000 |
| 96788998 | Ergocalciferol 400000units/ml oral solution | ml | 400000 |
| 97023992 | CALCIFEROL 100,000 IU/ML INJ | ml | 100000 |
| 97024992 | CALCIFEROL 600,000 IU/ML INJ | ml | 600000 |
| 97032992 | CALCIFEROL 300 IU/ML I/U SYR | ml | 300 |
| 97033992 | CALCIFEROL DROPS LIQ | ml | - |
| 97034992 | CALCIFEROL 400 I/U INJ | ml | 400 |
| 97035992 | CALCIFEROL 9,000 IU/ML LIQ | ml | 9000 |
| 97036992 | CALCIFEROL 1,000 IU/5ML SOL | ml | 200 |
| 97037992 | CALCIFEROL 300 MG TAB | tablet / cap | 12000 |
| 97038992 | CALCIFEROL 15 MCG TAB | tablet / cap | 600 |
| 97238989 | Ergocalciferol 1.25mg tablets | tablet / cap | 50000 |
| 97238990 | Ergocalciferol 250microgram tablets | tablet / cap | 10000 |
| 97767998 | Calciferol BP 3000units/ml solution | ml | 3000 |
| 98374992 | VITAMIN D2 TAB | tablet / cap | - |
| 98421997 | Ergocalciferol 1.25mg tablets | tablet / cap | 50000 |
| 98421998 | Ergocalciferol 250microgram tablets | tablet / cap | 10000 |
| 98422997 | Ergocalciferol 1,000units/5ml oral suspension | ml | 200 |
| 98422998 | Ergocalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 98925998 | Calciferol 300,000 units/ml BP solution | ml | 300000 |
| 99763990 | Calciferol 300,000 units/ml BP solution | ml | 300000 |
| 59525978 | Colecalciferol 40,000unit capsules | tablet / cap | 40000 |
| 60566979 | Ergocalciferol 3,000units/ml oral solution sugar free | ml | 3000 |
| 73128978 | Colecalciferol 10,000unit capsules | tablet / cap | 10000 |
| 80018978 | Colecalciferol 1,000unit tablets | tablet / cap | 1000 |
| 73011978 | Colecalciferol 25,000units/ml oral solution sugar free 1ml unit dose ampoules | ml | 25000 |
| 83743978 | Ergocalciferol 1,000units/5ml oral solution | ml | 200 |
| 70249978 | Ergocalciferol 1.25mg capsules | tablet / cap | 50000 |
| 79935978 | Ergocalciferol 600,000units/1.5ml solution for injection ampoules | ml | 400000 |
| 73301978 | Colecalciferol 20,000units/ml oral solution | ml | 20000 |
| 99763988 | Ergocalciferol 250microgram tablets | tablet / cap | 10000 |
| 73012978 | Colecalciferol 25,000units/ml oral solution sugar free 1ml unit dose ampoules | ml | 25000 |
| 53321979 | Ergocalciferol 125microgram tablets | tablet / cap | 5000 |
| 83469978 | Colecalciferol 10,000unit tablets | tablet / cap | 10000 |
| 73392978 | Colecalciferol 3,200unit capsules | tablet / cap | 3200 |
| 60224979 | Colecalciferol 300,000units/1ml solution for injection ampoules | ml | 300000 |
| 54790979 | Ergocalciferol 1.25mg capsules | tablet / cap | 50000 |
| 59528978 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 62087979 | Colecalciferol 10,000units/ml oral solution | ml | 10000 |
| 60374979 | Colecalciferol 800unit capsules | tablet / cap | 800 |
| 60373979 | Colecalciferol 800unit capsules | tablet / cap | 800 |
| 73102978 | Colecalciferol 3,200unit capsules | tablet / cap | 3200 |
| 78388978 | Colecalciferol 500unit orodispersible tablets sugar free | tablet / cap | 500 |
| 78389978 | Colecalciferol 2,000unit orodispersible tablets sugar free | tablet / cap | 2000 |
| 59522978 | Colecalciferol 2,000unit tablets | tablet / cap | 2000 |
| 73391978 | Colecalciferol 3,200unit capsules | tablet / cap | 3200 |
| 53353979 | Colecalciferol 5,000unit tablets | tablet / cap | 5000 |
| 80151979 | Ergocalciferol 6,000units/5ml oral suspension | ml | 1200 |
| 78441978 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 83392978 | Colecalciferol 50,000unit tablets | tablet / cap | 50000 |
| 80019978 | Colecalciferol 1,000unit capsules | tablet / cap | 1000 |
| 78387978 | Colecalciferol 500unit orodispersible tablets sugar free | tablet / cap | 500 |
| 73129978 | Colecalciferol 20,000unit capsules | tablet / cap | 20000 |
| 53358979 | Colecalciferol 3,000unit capsules | tablet / cap | 3000 |

Abbreviations: IU, international units; cap, capsule

**Table G.2** Read codes related to ethnicity, nationality, country of birth, or language, coded using ONS 2001 Census classifications.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| **Codes referring to ethnicity, nationality, or race** | | | |
| 134..00 | Country of origin | - | - |
| 1341.00 | European origin | White | Other white |
| 1342.00 | African origin | Black | African |
| 1343.00 | Asian origin | Asian | - |
| 1344.00 | North American origin | White | Other white |
| 1345.00 | South American origin | Other | Other |
| 1346.00 | Australian origin | White | Other white |
| 1347.00 | Indian origin | Asian | Indian |
| 1348.00 | Middle Eastern origin | Other | Other |
| 1349.00 | Far Eastern origin | Other | Other |
| 134A.00 | West Indian origin | Black | Caribbean |
| 134B.00 | RACE: Caucasian | White | - |
| 134C.00 | RACE: Arab | Other | Other |
| 134D.00 | RACE: Chinese | Other | Chinese |
| 134E.00 | RACE: Japanese | Other | Other |
| 134F.00 | RACE: Korean | Other | Other |
| 134G.00 | RACE: Oriental | Other | Other |
| 134H.00 | RACE: Afro-caribbean | Black | - |
| 134I.00 | RACE: Bangladeshi | Asian | Bangladeshi |
| 134J.00 | RACE: Mixed | Mixed | - |
| 134K.00 | RACE: West indian | Black | Caribbean |
| 134L.00 | RACE: Afro-caucasian | Mixed | Other mixed |
| 134M.00 | RACE: Pakistani | Asian | Pakistani |
| 134N.00 | RACE: White | White | - |
| 134O.00 | RACE: Unknown | - | - |
| 134P.00 | RACE: Not stated | - | - |
| 134P.11 | RACE: Other | - | - |
| 134Z.00 | Country of origin NOS | - | - |
| 1X...00 | NHS Sickle Cell Thalassaemia Screening Program family | - | - |
| 1X0..00 | Sick Cell Thalas Scr Prog fam orig African or African | Black | African |
| 1X00.00 | NHS Sick Cell Thal Scr Prog Caribbean Islands family | Black | Caribbean |
| 1X01.00 | NHS Sick Cell Thalassaemia Screen Prog African family | Black | African |
| 1X1..00 | Sick Cell Thalas Scr Prog fam orig South Asia (Asian) | Asian | - |
| 1X10.00 | NHS Sic Cel Th Sc Prog India or African-Indian family | Asian | Indian |
| 1X11.00 | NHS Sickle Cell Thal Screening Prog Pakistan family o | Asian | Pakistani |
| 1X12.00 | NHS Sickle Cell Thal Screening Prog Bangladesh family | Asian | Bangladeshi |
| 1X2..00 | NHS Sick Cell Thal Scr Prog fam orig South East Asia | Other | Other |
| 1X20.00 | NHS Sickle Cel Thal Screening Program Chinese family | Other | Chinese |
| 1X21.00 | N Sic Cell Th Scr P Thailand, Indonesia, Burma family | Other | Other |
| 1X22.00 | NSCTSP Malaysia, Vietnam, Philippin, Cambodia, Laos f | Other | Other |
| 1X3..00 | NHS Sickle Cell Thal Scr Prog fam origin other non-Eu | - | - |
| 1X30.00 | NHS Sickle Cell Thalass Scr Prog North Africa family | Other | Other |
| 1X31.00 | NHS Sickle Cell Thal Scr Program South America family | Other | Other |
| 1X32.00 | NHS Sickle Cell Thal Scr Prog Middle East family orig | Other | Other |
| 1X4..00 | NHS Sic Cel Th Scr Prog fam orig Southern and other E | White | Other white |
| 1X40.00 | NHS Sickle Cell Thal Scr Prog Sardinia family origin | White | Other white |
| 1X41.00 | NSCTSP Greece, Turkey, Cyprus family origin | White | Other white |
| 1X42.00 | NSCTSP Italy, Portugal, Spain family origin | White | Other white |
| 1X5..00 | NHS Sick Cel Thal Scr Prog fam origin United Kingdom | White | British |
| 1X6..00 | NHS Sic Cel Thal Scr Prog fam orig Northern European | White | Other white |
| 1X60.00 | NSCTSP Austr, Belg, Ire, Fr, Germ, Netherland family | White | Other white |
| 1X61.00 | NSCTSP Scandinavia, Switzerland family origin | White | Other white |
| 226..00 | O/E - ethnic group | - | - |
| 226..11 | O/E - ethnic origin | - | - |
| 2261.00 | O/E - Europeanoid | White | - |
| 2262.00 | O/E - Negroid | Black | - |
| 2263.00 | O/E - Mongoloid origin | Other | Other |
| 2263.11 | O/E - Asian origin | Asian | - |
| 2264.00 | O/E - Australoid | Other | Other |
| 226Z.00 | O/E - ethnic group NOS | - | - |
| 916E.00 | Patient ethnicity unknown | - | - |
| 9S...00 | Ethnic groups (census) | - | - |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 9S1..00 | White | White | - |
| 9S10.00 | White British | White | British |
| 9S11.00 | White Irish | White | Irish |
| 9S12.00 | Other white ethnic group | White | Other white |
| 9S13.00 | White Scottish | White | British |
| 9S14.00 | Other white British ethnic group | White | British |
| 9S2..00 | Black Caribbean | Black | Caribbean |
| 9S3..00 | Black African | Black | African |
| 9S4..00 | Black, other, non-mixed origin | Black | Other black |
| 9S41.00 | Black British | Black | Other black |
| 9S42.00 | Black Caribbean/W.I./Guyana | Black | Caribbean |
| 9S42.11 | Black Caribbean | Black | Caribbean |
| 9S42.12 | Black West Indian | Black | Caribbean |
| 9S42.13 | Black Guyana | Black | Caribbean |
| 9S43.00 | Black N African/Arab/Iranian | Black | Other black |
| 9S43.11 | Black North African | Black | Other black |
| 9S43.12 | Black Arab | Black | Other black |
| 9S43.13 | Black Iranian | Black | Other black |
| 9S44.00 | Black - other African country | Black | African |
| 9S45.00 | Black E Afric Asia/Indo-Caribb | Black | Other black |
| 9S45.11 | Black East African Asian | Black | African |
| 9S45.12 | Black Indo-Caribbean | Black | Caribbean |
| 9S46.00 | Black Indian sub-continent | Black | Other black |
| 9S47.00 | Black - other Asian | Black | Other black |
| 9S48.00 | Black Black - other | Black | Other black |
| 9S5..00 | Black - other, mixed | Mixed | Other mixed |
| 9S51.00 | Other Black - Black/White orig | Mixed | Other mixed |
| 9S52.00 | Other Black - Black/Asian orig | Mixed | Other mixed |
| 9S6..00 | Indian | Asian | Indian |
| 9S7..00 | Pakistani | Asian | Pakistani |
| 9S8..00 | Bangladeshi | Asian | Bangladeshi |
| 9S9..00 | Chinese | Other | Chinese |
| 9SA..00 | Other ethnic non-mixed (NMO) | Other | Other |
| 9SA1.00 | Brit. ethnic minor. spec.(NMO) | - | - |
| 9SA2.00 | Brit. ethnic minor. unsp (NMO) | - | - |
| 9SA3.00 | Caribbean I./W.I./Guyana (NMO) | Black | Caribbean |
| 9SA3.11 | Caribbean Island (NMO) | Black | Caribbean |
| 9SA3.12 | West Indian (NMO) | Black | Caribbean |
| 9SA3.13 | Guyana (NMO) | Black | Caribbean |
| 9SA4.00 | N African Arab/Iranian (NMO) | Other | Other |
| 9SA4.11 | North African Arab (NMO) | Other | Other |
| 9SA4.12 | Iranian (NMO) | Other | Other |
| 9SA5.00 | Other African countries (NMO) | Black | African |
| 9SA6.00 | E Afric Asian/Indo-Carib (NMO) | Asian | Other Asian |
| 9SA6.11 | East African Asian (NMO) | Asian | Other Asian |
| 9SA6.12 | Indo-Caribbean (NMO) | Asian | Other Asian |
| 9SA7.00 | Indian sub-continent (NMO) | Asian | - |
| 9SA8.00 | Other Asian (NMO) | Asian | Other Asian |
| 9SA9.00 | Irish (NMO) | White | Irish |
| 9SAA.00 | Greek/Greek Cypriot (NMO) | White | Other white |
| 9SAA.11 | Greek (NMO) | White | Other white |
| 9SAA.12 | Greek Cypriot (NMO) | White | Other white |
| 9SAB.00 | Turkish/Turkish Cypriot (NMO) | White | Other white |
| 9SAB.11 | Turkish (NMO) | White | Other white |
| 9SAB.12 | Turkish Cypriot (NMO) | White | Other white |
| 9SAC.00 | Other European (NMO) | White | Other white |
| 9SAD.00 | Other ethnic NEC (NMO) | Other | Other |
| 9SB..00 | Other ethnic, mixed origin | Mixed | Other mixed |
| 9SB1.00 | Other ethnic, Black/White orig | Mixed | Other mixed |
| 9SB2.00 | Other ethnic, Asian/White orig | Mixed | White & Asian |
| 9SB3.00 | Other ethnic, mixed white orig | Mixed | Other mixed |
| 9SB4.00 | Other ethnic, other mixed orig | Mixed | Other mixed |
| 9SB5.00 | Black Caribbean and White | Mixed | White & Caribb. |
| 9SB6.00 | Black African and White | Mixed | White & African |
| 9SC..00 | Vietnamese | Other | Other |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 9SD..00 | Ethnic group not given - patient refused | - | - |
| 9SE..00 | Ethnic group not recorded | - | - |
| 9SG..00 | Other black ethnic group | Black | Other black |
| 9SH..00 | Other Asian ethnic group | Asian | Other Asian |
| 9SI..00 | Irish traveller | White | Other white |
| 9SJ..00 | Other ethnic group | Other | Other |
| 9SZ..00 | Ethnic groups (census) NOS | - | - |
| 9T...00 | Ethnicity and other related nationality data | - | - |
| 9T1..00 | New Zealand ethnic groups | - | - |
| 9T11.00 | New Zealand European | White | Other white |
| 9T11.11 | Pakeha | White | Other white |
| 9T12.00 | Other European in New Zealand | White | Other white |
| 9T13.00 | New Zealand Maori | Other | Other |
| 9T14.00 | Samoan | Other | Other |
| 9T15.00 | Cook Island Maori | Other | Other |
| 9T16.00 | Tongan | Other | Other |
| 9T17.00 | Niuean | Other | Other |
| 9T18.00 | Tokelauan | Other | Other |
| 9T19.00 | Fijian | Other | Other |
| 9T1A.00 | Other Pacific ethnic group | Other | Other |
| 9T1B.00 | South East Asian | Other | Other |
| 9T1C.00 | Chinese | Other | Chinese |
| 9T1D.00 | Indian | Asian | Indian |
| 9T1E.00 | Other Asian | Asian | Other Asian |
| 9T1Y.00 | Other New Zealand ethnic group | Other | Other |
| 9T1Z.00 | New Zealand ethnic group NOS | - | - |
| 9T2..00 | Traveller - gypsy | White | Other white |
| 9T3..00 | Yemeni | Other | Other |
| 9T4..00 | Romanian | White | Other white |
| 9T5..00 | Bulgarian | White | Other white |
| 9T6..00 | Czech | White | Other white |
| 9T7..00 | Slovak | White | Other white |
| 9T8..00 | Portuguese | White | Other white |
| 9T9..00 | Nepali | Asian | Other Asian |
| 9i...00 | Ethnic category - 2001 census | - | - |
| 9i0..00 | British or mixed British - ethnic category 2001 censu | White | British |
| 9i00.00 | White British - ethnic category 2001 census | White | British |
| 9i1..00 | Irish - ethnic category 2001 census | White | Irish |
| 9i10.00 | White Irish - ethnic category 2001 census | White | Irish |
| 9i2..00 | Other White background - ethnic category 2001 census | White | Other white |
| 9i20.00 | English - ethnic category 2001 census | White | British |
| 9i21.00 | Scottish - ethnic category 2001 census | White | British |
| 9i22.00 | Welsh - ethnic category 2001 census | White | British |
| 9i23.00 | Cornish - ethnic category 2001 census | White | British |
| 9i24.00 | Northern Irish - ethnic category 2001 census | White | Other white |
| 9i25.00 | Ulster Scots - ethnic category 2001 census | White | Other white |
| 9i26.00 | Cypriot (part not stated) – ethnic category 2001 cens | White | Other white |
| 9i27.00 | Greek – ethnic category 2001 census | White | Other white |
| 9i28.00 | Greek Cypriot – ethnic category 2001 census | White | Other white |
| 9i29.00 | Turkish – ethnic category 2001 census | White | Other white |
| 9i2A.00 | Turkish Cypriot – ethnic category 2001 census | White | Other white |
| 9i2B.00 | Italian – ethnic category 2001 census | White | Other white |
| 9i2C.00 | Irish Traveller – ethnic category 2001 census | White | Other white |
| 9i2D.00 | Traveller – ethnic category 2001 census | White | Other white |
| 9i2E.00 | Gypsy/Romany – ethnic category 2001 census | White | Other white |
| 9i2F.00 | Polish – ethnic category 2001 census | White | Other white |
| 9i2G.00 | Baltic Estonian/Latvian/Lithuanian – ethn categ 2001 | White | Other white |
| 9i2H.00 | Commonwealth (Russian) Indep States – ethn categ 2001 | White | Other white |
| 9i2J.00 | Kosovan – ethnic category 2001 census | White | Other white |
| 9i2K.00 | Albanian – ethnic category 2001 census | White | Other white |
| 9i2L.00 | Bosnian – ethnic category 2001 census | White | Other white |
| 9i2M.00 | Croatian – ethnic category 2001 census | White | Other white |
| 9i2N.00 | Serbian – ethnic category 2001 census | White | Other white |
| 9i2P.00 | Other republics former Yugoslavia – ethnic categ 2001 | White | Other white |
| 9i2Q.00 | Mixed Irish and other White – ethnic category 2001 ce | White | Other white |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 9i2R.00 | Oth White European/European unsp/Mixed European 2001 | White | Other white |
| 9i2S.00 | Other mixed White – ethnic category 2001 census | White | Other white |
| 9i2T.00 | Other White or White unspecified ethnic category 2001 | White | Other white |
| 9i3..00 | White and Black Caribbean – ethnic category 2001 cens | Mixed | White & Caribb. |
| 9i4..00 | White and Black African – ethnic category 2001 census | Mixed | White & African |
| 9i5..00 | White and Asian – ethnic category 2001 census | Mixed | White & Asian |
| 9i6..00 | Other Mixed background – ethnic category 2001 census | Mixed | Other mixed |
| 9i60.00 | Black and Asian – ethnic category 2001 census | Mixed | Other mixed |
| 9i61.00 | Black and Chinese – ethnic category 2001 census | Mixed | Other mixed |
| 9i62.00 | Black and White – ethnic category 2001 census | Mixed | Other mixed |
| 9i63.00 | Chinese and White – ethnic category 2001 census | Mixed | Other mixed |
| 9i64.00 | Asian and Chinese – ethnic category 2001 census | Mixed | Other mixed |
| 9i65.00 | Other Mixed or Mixed unspecified ethnic category 2001 | Mixed | Other mixed |
| 9i7..00 | Indian or British Indian – ethnic category 2001 censu | Asian | Indian |
| 9i8..00 | Pakistani or British Pakistani – ethnic category 2001 | Asian | Pakistani |
| 9i9..00 | Bangladeshi or British Bangladeshi – ethn categ 2001 | Asian | Bangladeshi |
| 9iA..00 | Other Asian background – ethnic category 2001 census | Asian | Other Asian |
| 9iA1.00 | Punjabi – ethnic category 2001 census | Asian | Other Asian |
| 9iA2.00 | Kashmiri – ethnic category 2001 census | Asian | Other Asian |
| 9iA3.00 | East African Asian – ethnic category 2001 census | Asian | Other Asian |
| 9iA4.00 | Sri Lankan – ethnic category 2001 census | Asian | Other Asian |
| 9iA5.00 | Tamil – ethnic category 2001 census | Asian | Other Asian |
| 9iA6.00 | Sinhalese – ethnic category 2001 census | Asian | Other Asian |
| 9iA7.00 | Caribbean Asian – ethnic category 2001 census | Asian | Other Asian |
| 9iA8.00 | British Asian – ethnic category 2001 census | Asian | Other Asian |
| 9iA9.00 | Mixed Asian – ethnic category 2001 census | Asian | Other Asian |
| 9iAA.00 | Other Asian or Asian unspecified ethnic category 2001 | Asian | Other Asian |
| 9iB..00 | Caribbean – ethnic category 2001 census | Black | Caribbean |
| 9iC..00 | African – ethnic category 2001 census | Black | African |
| 9iD..00 | Other Black background – ethnic category 2001 census | Black | Other black |
| 9iD0.00 | Somali – ethnic category 2001 census | Black | African |
| 9iD1.00 | Nigerian – ethnic category 2001 census | Black | African |
| 9iD2.00 | Black British – ethnic category 2001 census | Black | Other black |
| 9iD3.00 | Mixed Black – ethnic category 2001 census | Black | Other black |
| 9iD4.00 | Other Black or Black unspecified ethnic category 2001 | Black | Other black |
| 9iE..00 | Chinese – ethnic category 2001 census | Other | Chinese |
| 9iF..00 | Other – ethnic category 2001 census | Other | Other |
| 9iF0.00 | Vietnamese – ethnic category 2001 census | Other | Other |
| 9iF1.00 | Japanese – ethnic category 2001 census | Other | Other |
| 9iF2.00 | Filipino – ethnic category 2001 census | Other | Other |
| 9iF3.00 | Malaysian – ethnic category 2001 census | Other | Other |
| 9iF4.00 | Buddhist – ethnic category 2001 census | - | - |
| 9iF5.00 | Hindu – ethnic category 2001 census | - | - |
| 9iF6.00 | Jewish – ethnic category 2001 census | - | - |
| 9iF7.00 | Muslim – ethnic category 2001 census | - | - |
| 9iF8.00 | Sikh – ethnic category 2001 census | - | - |
| 9iF9.00 | Arab - ethnic category 2001 census | Other | Other |
| 9iFA.00 | North African - ethnic category 2001 census | Other | Other |
| 9iFB.00 | Mid East (excl Israeli, Iranian & Arab) - eth cat 200 | Other | Other |
| 9iFC.00 | Israeli - ethnic category 2001 census | Other | Other |
| 9iFD.00 | Iranian - ethnic category 2001 census | Other | Other |
| 9iFE.00 | Kurdish - ethnic category 2001 census | Other | Other |
| 9iFF.00 | Moroccan - ethnic category 2001 census | Other | Other |
| 9iFG.00 | Latin American - ethnic category 2001 census | Other | Other |
| 9iFH.00 | South and Central American - ethnic category 2001 cen | Other | Other |
| 9iFJ.00 | Mauritian/Seychellois/Maldivian/St Helena eth cat 200 | Other | Other |
| 9iFK.00 | Any other group - ethnic category 2001 census | Other | Other |
| 9iG..00 | Ethnic category not stated - 2001 census | - | - |
| **Codes referring to country of birth** | | | |
| 134..11 | Born in - country | - | - |
| 13d..00 | Country of birth (European) | - | - |
| 13d0.00 | Born in Albania | White | Other white |
| 13d1.00 | Born in Andorra | White | Other white |
| 13d2.00 | Born in Austria | White | Other white |
| 13d3.00 | Born in Azerbaijan | Other | Other |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13d4.00 | Born in Belgium | White | Other white |
| 13d5.00 | Born in Belorussia | White | Other white |
| 13d6.00 | Born in Bosnia - Herzegovnia | White | Other white |
| 13d7.00 | Born in Bulgaria | White | Other white |
| 13d8.00 | Born in Croatia | White | Other white |
| 13d9.00 | Born in Cyprus | White | Other white |
| 13dA.00 | Born in Czech Republic | White | Other white |
| 13dB.00 | Born in Denmark | White | Other white |
| 13dC.00 | Born in England | - | - |
| 13dD.00 | Born in Estonia | White | Other white |
| 13dE.00 | Born in Finland | White | Other white |
| 13dF.00 | Born in France | White | Other white |
| 13dG.00 | Born in Germany | White | Other white |
| 13dH.00 | Born in Greece | White | Other white |
| 13dI.00 | Born in Hungary | White | Other white |
| 13dJ.00 | Born in Iceland | White | Other white |
| 13dK.00 | Born in Ireland | White | Irish |
| 13dL.00 | Born in Italy | White | Other white |
| 13dM.00 | Born in Kosovo | White | Other white |
| 13dN.00 | Born in Latvia | White | Other white |
| 13dO.00 | Born in Liechtenstein | White | Other white |
| 13dP.00 | Born in Lithuania | White | Other white |
| 13dQ.00 | Born in Luxembourg | White | Other white |
| 13dR.00 | Born in Malta | White | Other white |
| 13dS.00 | Born in Moldavia | White | Other white |
| 13dT.00 | Born in Monaco | White | Other white |
| 13dU.00 | Born in Northern Ireland | White | Other white |
| 13dV.00 | Born in Norway | White | Other white |
| 13dW.00 | Born in Poland | White | Other white |
| 13dX.00 | Born in Portugal | White | Other white |
| 13dY.00 | Born in Republic of Ireland | White | Irish |
| 13dZ.00 | Born in Romania | White | Other white |
| 13da.00 | Born in San Marino | White | Other white |
| 13db.00 | Born in Scotland | White | British |
| 13dc.00 | Born in Slovakia | White | Other white |
| 13dd.00 | Born in Slovenia | White | Other white |
| 13de.00 | Born in Spain | White | Other white |
| 13df.00 | Born in Sweden | White | Other white |
| 13dg.00 | Born in Switzerland | White | Other white |
| 13dh.00 | Born in The Netherlands | White | Other white |
| 13di.00 | Born in Ukraine | White | Other white |
| 13dj.00 | Born in Vatican City | White | Other white |
| 13dk.00 | Born in Wales | White | British |
| 13dl.00 | Born in Yugoslavia | White | Other white |
| 13dm.00 | Born in former Yugoslav Republic of Macedonia | White | Other white |
| 13dn.00 | Born in Serbia | White | Other white |
| 13e..00 | Country of birth (Asian) | - | - |
| 13e0.00 | Born in Afghanistan | Other | Other |
| 13e1.00 | Born in Armenia | White | Other white |
| 13e2.00 | Born in Bahrain | Other | Other |
| 13e3.00 | Born in Bangladesh | Asian | Bangladeshi |
| 13e4.00 | Born in Bhutan | Other | Other |
| 13e5.00 | Born in Brunei | Other | Other |
| 13e6.00 | Born in Burma | Other | Other |
| 13e7.00 | Born in Chechnya | White | Other white |
| 13e8.00 | Born in China | Other | Chinese |
| 13e9.00 | Born in Democratic People's Republic of Korea | Other | Other |
| 13eA.00 | Born in East Timor | Other | Other |
| 13eB.00 | Born in Georgia | White | Other white |
| 13eC.00 | Born in Hong Kong | Other | Chinese |
| 13eD.00 | Born in India | Asian | Indian |
| 13eE.00 | Born in Indonesia | Other | Other |
| 13eF.00 | Born in Iran | Other | Other |
| 13eG.00 | Born in Iraq | Other | Other |
| 13eH.00 | Born in Israel | Other | Other |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13eI.00 | Born in Japan | Other | Other |
| 13eJ.00 | Born in Jordan | Other | Other |
| 13eK.00 | Born in Kazakhstan | Other | Other |
| 13eL.00 | Born in Kuwait | Other | Other |
| 13eM.00 | Born in Kyrgyzstan | Other | Other |
| 13eN.00 | Born in Laos | Other | Other |
| 13eO.00 | Born in Lebanon | Other | Other |
| 13eP.00 | Born in Malaysia | Other | Other |
| 13eQ.00 | Born in Maldives | Other | Other |
| 13eR.00 | Born in Mali | Other | Other |
| 13eS.00 | Born in Mongolia | Other | Other |
| 13eT.00 | Born in Nepal | Asian | Other Asian |
| 13eU.00 | Born in North Korea | Other | Other |
| 13eV.00 | Born in Oman | Other | Other |
| 13eW.00 | Born in Pakistan | Asian | Pakistani |
| 13eX.00 | Born in Palestine | Other | Other |
| 13eY.00 | Born in Philippines | Other | Other |
| 13eZ.00 | Born in Qatar | Other | Other |
| 13ea.00 | Born in Republic of Korea | Other | Other |
| 13eb.00 | Born in Russia | White | Other white |
| 13ec.00 | Born in Saudi Arabia | Other | Other |
| 13ed.00 | Born in Singapore | Other | Other |
| 13ee.00 | Born in South Korea | Other | Other |
| 13ef.00 | Born in Sri Lanka | Asian | Other Asian |
| 13eg.00 | Born in Syria | Other | Other |
| 13eh.00 | Born in Taiwan | Other | Other |
| 13ei.00 | Born in Tajikistan | Other | Other |
| 13ej.00 | Born in Thailand | Other | Other |
| 13ek.00 | Born in Turkey | White | Other white |
| 13el.00 | Born in Turkmenistan | Other | Other |
| 13em.00 | Born in United Arab Emirates | Other | Other |
| 13en.00 | Born in Uzbekistan | Other | Other |
| 13eo.00 | Born in Vietnam | Other | Other |
| 13ep.00 | Born in Yemen | Other | Other |
| 13f..00 | Country of birth (American) | - | - |
| 13f0.00 | Born in Argentina | Other | Other |
| 13f1.00 | Born in Belize | Other | Other |
| 13f2.00 | Born in Bolivia | Other | Other |
| 13f3.00 | Born in Brazil | Other | Other |
| 13f4.00 | Born in British Guyana | Other | Other |
| 13f5.00 | Born in Canada | White | Other white |
| 13f6.00 | Born in Chile | Other | Other |
| 13f7.00 | Born in Columbia | Other | Other |
| 13f8.00 | Born in Costa Rica | Other | Other |
| 13f9.00 | Born in Ecuador | Other | Other |
| 13fA.00 | Born in El Salvador | Other | Other |
| 13fB.00 | Born in Grenada | Other | Other |
| 13fC.00 | Born in Guatemala | Other | Other |
| 13fD.00 | Born in Guyana | Other | Other |
| 13fE.00 | Born in Honduras | Other | Other |
| 13fF.00 | Born in Mexico | Other | Other |
| 13fG.00 | Born in Nicaragua | Other | Other |
| 13fH.00 | Born in Panama | Other | Other |
| 13fI.00 | Born in Paraguay | Other | Other |
| 13fJ.00 | Born in Peru | Other | Other |
| 13fK.00 | Born in Suriname | Other | Other |
| 13fL.00 | Born in USA | White | Other white |
| 13fM.00 | Born in Uruguay | Other | Other |
| 13fN.00 | Born in Venezuela | Other | Other |
| 13g..00 | Country of birth (African) | - | - |
| 13g0.00 | Born in Algeria | Other | Other |
| 13g1.00 | Born in Angola | Black | African |
| 13g2.00 | Born in Benin | Black | African |
| 13g3.00 | Born in Botswana | Black | African |
| 13g4.00 | Born in Burkina Faso | Black | African |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13g5.00 | Born in Burundi | Black | African |
| 13g6.00 | Born in Cambodia | Other | Other |
| 13g7.00 | Born in Cameroon | Black | African |
| 13g8.00 | Born in Cape Verde Islands | Black | African |
| 13g9.00 | Born in Central African Republic | Black | African |
| 13gA.00 | Born in Chad | Black | African |
| 13gB.00 | Born in Comoros Islands | Black | African |
| 13gC.00 | Born in Congo | Black | African |
| 13gD.00 | Born in Djibouti | Black | African |
| 13gE.00 | Born in Egypt | Other | Other |
| 13gF.00 | Born in Equatorial Guinea | Black | African |
| 13gG.00 | Born in Ethiopia | Black | African |
| 13gH.00 | Born in Gabon | Black | African |
| 13gI.00 | Born in Gambia | Black | African |
| 13gJ.00 | Born in Ghana | Black | African |
| 13gK.00 | Born in Guinea Bissau | Black | African |
| 13gL.00 | Born in Guinea Republic | Black | African |
| 13gM.00 | Born in Ivory Coast | Black | African |
| 13gN.00 | Born in Kenya | Black | African |
| 13gO.00 | Born in Lesotho | Black | African |
| 13gP.00 | Born in Liberia | Black | African |
| 13gQ.00 | Born in Libya | Other | Other |
| 13gR.00 | Born in Madagascar | Black | African |
| 13gS.00 | Born in Malawi | Black | African |
| 13gT.00 | Born in Mauritania | Black | African |
| 13gU.00 | Born in Mauritius | Asian | Other Asian |
| 13gV.00 | Born in Morocco | Other | Other |
| 13gW.00 | Born in Mozambique | Black | African |
| 13gX.00 | Born in Namibia | Black | African |
| 13gY.00 | Born in Niger | Black | African |
| 13gZ.00 | Born in Nigeria | Black | African |
| 13ga.00 | Born in Rwanda | Black | African |
| 13gb.00 | Born in Sao Tome and Principe | Black | African |
| 13gc.00 | Born in Senegal | Black | African |
| 13gd.00 | Born in Sierra Leone | Black | African |
| 13ge.00 | Born in Somalia | Black | African |
| 13gf.00 | Born in South Africa | - | - |
| 13gg.00 | Born in Sudan | Other | Other |
| 13gh.00 | Born in Swaziland | Black | African |
| 13gi.00 | Born in Tanzania | Black | African |
| 13gj.00 | Born in The Gambia | Black | African |
| 13gk.00 | Born in Tunisia | Other | Other |
| 13gl.00 | Born in Uganda | Black | African |
| 13gm.00 | Born in Zaire | Black | African |
| 13gn.00 | Born in Zambia | Black | African |
| 13go.00 | Born in Zimbabwe | Black | African |
| 13gp.00 | Born in Eritrea | Black | African |
| 13h..00 | Country of birth (Australasian) | - | - |
| 13h0.00 | Born in Australia | White | Other white |
| 13h1.00 | Born in New Zealand | White | Other white |
| 13j..00 | Country of birth (Atlantic) | - | - |
| 13j0.00 | Born in Antigua and Barbuda | Black | Caribbean |
| 13j1.00 | Born in Bahamas | Black | Caribbean |
| 13j2.00 | Born in Barbados | Black | Caribbean |
| 13j3.00 | Born in Cuba | Black | Caribbean |
| 13j4.00 | Born in Dominican Republic | Black | Caribbean |
| 13j5.00 | Born in Haiti | Black | Caribbean |
| 13j6.00 | Born in Jamaica | Black | Caribbean |
| 13j7.00 | Born in Puerto Rico | Black | Caribbean |
| 13j8.00 | Born in St. Kitts and Nevis | Black | Caribbean |
| 13j9.00 | Born in St. Lucia | Black | Caribbean |
| 13jA.00 | Born in St. Vincent | Black | Caribbean |
| 13jB.00 | Born in Togo | Black | African |
| 13jC.00 | Born in Trinidad and Tobago | Black | Caribbean |
| 13jD.00 | Born in Dominica | Black | Caribbean |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13jE.00 | Born in Aruba | Black | Caribbean |
| 13k..00 | Country of birth (Pacific) | - | - |
| 13k0.00 | Born in Fiji | Other | Other |
| 13k1.00 | Born in Kiribati | Other | Other |
| 13k2.00 | Born in Nauru | Other | Other |
| 13k3.00 | Born in Papua New Guinea | Other | Other |
| 13k4.00 | Born in Seychelles | Other | Other |
| 13k5.00 | Born in Solomon Islands | Other | Other |
| 13k6.00 | Born in Tonga | Other | Other |
| 13k7.00 | Born in Tuvalu | Other | Other |
| 13k8.00 | Born in Vanuatu | Other | Other |
| 13k9.00 | Born in Western Samoa | Other | Other |
| 13t..00 | Born in British overseas territory | - | - |
| 13t0.00 | Born in Montserrat | - | - |
| 13t1.00 | Born in Bermuda | - | - |
| 13t2.00 | Born in Anguilla | - | - |
| 13v..00 | Born French overseas region department collectivity t | - | - |
| 13v0.00 | Born in Martinique | Black | Caribbean |
| 13do.00 | Born in Montenegro | White | Other white |
| 13dp.00 | Born in Belarus | White | Other white |
| 13dq.00 | Born in Republic of Moldova | White | Other white |
| 13dr.00 | Born in Guernsey | White | British |
| 13ds.00 | Born in Jersey | White | British |
| 13dt.00 | Born in Isle of Man | White | British |
| 13du.00 | Born in Faroe Islands | White | Other white |
| 13dv.00 | Born in Greenland | White | Other white |
| 13dw.00 | Born in Svalbard and Jan Mayen | White | Other white |
| 13dx.00 | Born in Aland Islands | White | Other white |
| 13eq.00 | Born in Christmas Island | Other | Chinese |
| 13er.00 | Born in Cocos (Keeling) Islands | Other | Other |
| 13es.00 | Born in Macao | Other | Chinese |
| 13gq.00 | Born in Democratic Republic of Congo | Black | African |
| 13gr.00 | Born in Western Sahara | Other | Other |
| 13jF.00 | Born in United States Virgin Islands | Black | Caribbean |
| 13jG.00 | Born in Saint Vincent and the Grenadines | Black | Caribbean |
| 13jH.00 | Born in Sint Maarten | Black | Caribbean |
| 13jJ.00 | Born in Saint-Martin | Black | Caribbean |
| 13jK.00 | Born in Bonaire, Sint Eustatius and Saba | Black | Caribbean |
| 13jL.00 | Born in Curacao | Black | Caribbean |
| 13kA.00 | Born in Samoa | Other | Other |
| 13kB.00 | Born in American Samoa | Other | Other |
| 13kC.00 | Born in United States Minor Outlying Islands | - | - |
| 13kD.00 | Born in Tokelau | Other | Other |
| 13kE.00 | Born in Cook Islands | Other | Other |
| 13kF.00 | Born in Guam | Other | Other |
| 13kG.00 | Born in Federated States of Micronesia | Other | Other |
| 13kH.00 | Born in Marshall Islands | Other | Other |
| 13kJ.00 | Born in Niue | Other | Other |
| 13kK.00 | Born in Norfolk Island | White | Other white |
| 13kL.00 | Born in Northern Mariana Islands | Other | Other |
| 13kM.00 | Born in Palau | Other | Other |
| 13kN.00 | Born in Antarctica | - | - |
| 13t3.00 | Born in British Virgin Islands | Black | Caribbean |
| 13t4.00 | Born in Turks and Caicos Islands | Black | Caribbean |
| 13t5.00 | Born in Saint Helena, Ascension and Tristan da Cunha | Black | Caribbean |
| 13t6.00 | Born in South Georgia and the South Sandwich Islands | - | - |
| 13t7.00 | Born in Falkland Islands | White | British |
| 13t8.00 | Born in British Indian Ocean Territory | - | - |
| 13t9.00 | Born in Cayman Islands | Mixed | White & African |
| 13tA.00 | Born in Pitcairn Islands | White | Other white |
| 13v1.00 | Born in Saint Pierre and Miquelon | White | Other white |
| 13v2.00 | Born in Wallis and Futuna | Other | Other |
| 13v3.00 | Born in French Polynesia | Other | Other |
| 13v4.00 | Born in French Guiana | Other | Other |
| 13v5.00 | Born in French Southern Territories | - | - |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13v6.00 | Born in Mayotte | Other | Other |
| 13v7.00 | Born in Guadeloupe | Black | Caribbean |
| 13v8.00 | Born in Reunion | - | - |
| 13v9.00 | Born in New Caledonia | Other | Other |
| **Codes referring to spoken or read language, or the need for an interpreter** | | | |
| 13Z6.00 | Language spoken | - | - |
| 13Z6.11 | Language | - | - |
| 13Z6000 | English as a second language | - | - |
| 13Z6100 | Language Bengali | Asian | - |
| 13Z6200 | Language Gujurati | Asian | - |
| 13Z6300 | Language Hindi | Asian | - |
| 13Z6400 | Language Pashtu | Other | Other |
| 13Z6500 | Language Punjabi | Asian | - |
| 13Z6600 | Language Urdu | Asian | - |
| 13Z6700 | Speaks English well | - | - |
| 13Z6800 | Speaks English poorly | - | - |
| 13Z6Z00 | Language NOS | - | - |
| 13b..00 | World languages | - | - |
| 13b0.00 | Vietnamese language | Other | Other |
| 13b1.00 | Cantonese Chinese dialect | Other | Chinese |
| 13b2.00 | Sylhety | Asian | - |
| 13b3.00 | Creole language | - | - |
| 13b4.00 | Mirpuri language | Asian | - |
| 13l..00 | Main spoken language | - | - |
| 13l0.00 | Main spoken language Arabic | - | - |
| 13l1.00 | Main spoken language Bengali | Asian | - |
| 13l2.00 | Main spoken language Cantonese | Other | Chinese |
| 13l3.00 | Main spoken language Czech | White | Other white |
| 13l4.00 | Main spoken language English | - | - |
| 13l5.00 | Main spoken language French | - | - |
| 13l6.00 | Main spoken language Gujerati | Asian | - |
| 13l7.00 | Main spoken language Hausa | Black | African |
| 13l8.00 | Main spoken language Hindi | Asian | - |
| 13l9.00 | Main spoken language Iba | - | - |
| 13l9.11 | Main spoken language Iban | Other | Other |
| 13lA.00 | Main spoken language Kutchi | Asian | - |
| 13lB.00 | Main spoken language Mandarin | Other | Chinese |
| 13lC.00 | Main spoken language Polish | White | Other white |
| 13lD.00 | Main spoken language Portuguese | - | - |
| 13lE.00 | Main spoken language Punjabi | Asian | - |
| 13lE.11 | Main spoken language Panjabi | Asian | - |
| 13lF.00 | Main spoken language Russian | White | Other white |
| 13lG.00 | Main spoken language Somali | Black | African |
| 13lH.00 | Main spoken language Spanish | - | - |
| 13lI.00 | Main spoken language Swahili | Black | African |
| 13lJ.00 | Main spoken language Sylheti | Asian | - |
| 13lK.00 | Main spoken language Tamil | Asian | - |
| 13lL.00 | Main spoken language Urdu | Asian | - |
| 13lM.00 | Main spoken language Yoruba | Black | African |
| 13lN.00 | Main spoken language Kurdish | Other | Other |
| 13lO.00 | Main spoken language Farsi | Other | Other |
| 13lO.11 | Main spoken language Persian | Other | Other |
| 13lP.00 | Main spoken language Shona | Black | African |
| 13lQ.00 | Main spoken language Italian | White | Other white |
| 13lR.00 | Main spoken language German | White | Other white |
| 13lS.00 | Main spoken language Albanian | White | Other white |
| 13lT.00 | Main spoken language Croatian | White | Other white |
| 13lT.11 | Main spoken language Serbo-Croatian | White | Other white |
| 13lV.00 | Main spoken language Greek | White | Other white |
| 13lW.00 | Main spoken language Japanese | Other | Other |
| 13lX.00 | Main spoken language Korean | Other | Other |
| 13lY.00 | Main spoken language Lithuanian | White | Other white |
| 13lZ.00 | Main spoken language Turkish | White | Other white |
| 13la.00 | Main spoken language Ukrainian | White | Other white |
| 13lc.00 | Main spoken language Akan | Black | African |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13ld.00 | Main spoken language Amharic | Black | African |
| 13le.00 | Main spoken language Brawa | Black | African |
| 13lf.00 | Main spoken language Dutch | White | Other white |
| 13lg.00 | Main spoken language Ethiopian | Black | African |
| 13lh.00 | Main spoken language Flemish | White | Other white |
| 13li.00 | Main spoken language French Creole | - | - |
| 13lj.00 | Main spoken language Gaelic | White | - |
| 13lk.00 | Main spoken language Hakka | Asian | - |
| 13ll.00 | Main spoken language Hebrew | - | - |
| 13lm.00 | Main spoken language Igbo | Black | African |
| 13ln.00 | Main spoken language Lingala | Black | African |
| 13lo.00 | Main spoken language Luganda | Black | African |
| 13lp.00 | Main spoken language Malayalam | Asian | - |
| 13lq.00 | Main spoken language Norwegian | White | Other white |
| 13lr.00 | Main spoken language Pashto | Other | Other |
| 13ls.00 | Main spoken language Patois | - | - |
| 13lt.00 | Main spoken language Serbian | White | Other white |
| 13lt.11 | Main spoken language Serbo-Croatian | White | Other white |
| 13lu.00 | Main spoken language Sinhala | Asian | - |
| 13lu.11 | Main spoken language Sinhalese | Asian | - |
| 13lv.00 | Main spoken language Swedish | White | Other white |
| 13lw.00 | Main spoken language Tagalog | Other | Other |
| 13lx.00 | Main spoken language Thai | Other | Other |
| 13ly.00 | Main spoken language Tigrinya | Black | African |
| 13lz.00 | Main spoken language Welsh | White | British |
| 13n..00 | Language read | - | - |
| 13n0.00 | Reads Arabic | - | - |
| 13n1.00 | Reads Portuguese | - | - |
| 13n2.00 | Reads Punjabi | Asian | - |
| 13n3.00 | Reads Russian | White | Other white |
| 13n4.00 | Reads Somali | Black | African |
| 13n5.00 | Reads Spanish | - | - |
| 13n6.00 | Reads Tamil | Asian | - |
| 13n7.00 | Reads Urdu | Asian | - |
| 13n8.00 | Reads Bengali | Asian | - |
| 13n9.00 | Reads Cantonese | Other | Chinese |
| 13nA.00 | Reads Czech | White | Other white |
| 13nB.00 | Reads English | - | - |
| 13nC.00 | Reads French | - | - |
| 13nD.00 | Reads Hindi | Asian | - |
| 13nE.00 | Reads Chinese | Other | Chinese |
| 13nF.00 | Reads Polish | White | Other white |
| 13nG.00 | Reads Lithuanian | White | Other white |
| 13nH.00 | Reads Farsi | Other | Other |
| 13nJ.00 | Reads Chinese - Traditional | Other | Chinese |
| 13nK.00 | Reads Gujarati | Asian | - |
| 13nL.00 | Reads Hausa | Black | African |
| 13nM.00 | Reads Chinese - Simplified | Other | Chinese |
| 13nN.00 | Reads Swahili | Black | African |
| 13nP.00 | Reads Yoruba | Black | African |
| 13nQ.00 | Reads Kurdish | Other | Other |
| 13nR.00 | Reads Italian | White | Other white |
| 13nS.00 | Reads German | White | Other white |
| 13nT.00 | Reads Albanian | White | Other white |
| 13nV.00 | Reads Croatian | White | Other white |
| 13nW.00 | Reads Greek | White | Other white |
| 13nX.00 | Reads Japanese | Other | Other |
| 13nY.00 | Reads Turkish | White | Other white |
| 13nZ.00 | Reads Vietnamese | Other | Other |
| 13na.00 | Reads Amharic | Black | African |
| 13nb.00 | Reads Lingala | Black | African |
| 13nc.00 | Reads Pashto | Other | Other |
| 13nd.00 | Reads Serbian | White | Other white |
| 13ne.00 | Reads Sinhala | Asian | - |
| 13nf.00 | Reads Tigrinya | Black | African |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13ng.00 | Reads Bulgarian | White | Other white |
| 13nh.00 | Reads Burmese | Other | Other |
| 13ni.00 | Reads Chechen | White | Other white |
| 13nj.00 | Reads Indonesian | Other | Other |
| 13nk.00 | Reads Kinyarwanda | Black | African |
| 13nl.00 | Reads Kurmanji | Other | Other |
| 13nm.00 | Reads Malay | Other | Other |
| 13nn.00 | Reads Mongolian | Other | Other |
| 13no.00 | Reads Ndebele | Black | African |
| 13np.00 | Reads Braille | - | - |
| 13nq.00 | Reads Welsh | White | British |
| 13s..00 | Second language | - | - |
| 13s0.00 | Akan as a second language | Black | African |
| 13s1.00 | Albanian as a second language | White | Other white |
| 13s2.00 | Amharic as a second language | Black | African |
| 13s3.00 | Arabic as a second language | - | - |
| 13s4.00 | Bengali as a second language | Asian | - |
| 13s5.00 | Italian as a second language | White | Other white |
| 13s6.00 | Chinese as a second language | Other | Chinese |
| 13s7.00 | Croatian as a second language | White | Other white |
| 13s8.00 | Czech as a second language | White | Other white |
| 13s9.00 | Dutch as a second language | White | Other white |
| 13sA.00 | English as a second language | - | - |
| 13sB.00 | German as a second language | White | Other white |
| 13sC.00 | Ukrainian as a second language | White | Other white |
| 13sD.00 | French as a second language | - | - |
| 13sE.00 | Vietnamese as a second language | Other | Other |
| 13sF.00 | Irish Gaelic as a second language | White | Irish |
| 13sG.00 | Greek as a second language | White | Other white |
| 13sH.00 | Gujarati as a second language | Asian | - |
| 13sI.00 | Tamil as a second language | Asian | - |
| 13sJ.00 | Urdu as a second language | Asian | - |
| 13sK.00 | Hausa as a second language | Black | African |
| 13sL.00 | Hebrew as a second language | - | - |
| 13sM.00 | Hindi as a second language | Asian | - |
| 13sN.00 | Yoruba as a second language | Black | African |
| 13sO.00 | Tagalog as a second language | Other | Other |
| 13sP.00 | Igbo as a second language | Black | African |
| 13sQ.00 | Japanese as a second language | Other | Other |
| 13sR.00 | Korean as a second language | Other | Other |
| 13sS.00 | Kurdish as a second language | Other | Other |
| 13sT.00 | Lingala as a second language | Black | African |
| 13sU.00 | Turkish as a second language | White | Other white |
| 13sV.00 | Lithuanian as a second language | White | Other white |
| 13sW.00 | Shona as a second language | Black | African |
| 13sX.00 | Malayalam as a second language | Asian | - |
| 13sY.00 | Norwegian as a second language | White | Other white |
| 13sZ.00 | Polish as a second language | White | Other white |
| 13sa.00 | Portuguese as a second language | - | - |
| 13sb.00 | Thai as a second language | Other | Other |
| 13sc.00 | Russian as a second language | White | Other white |
| 13sd.00 | Serbian as a second language | White | Other white |
| 13se.00 | Tigrinya as a second language | Black | African |
| 13sf.00 | Somali as a second language | Black | African |
| 13sg.00 | Spanish as a second language | - | - |
| 13sh.00 | Swahili as a second language | Black | African |
| 13si.00 | Swedish as a second language | White | Other white |
| 13sj.00 | Welsh as a second language | White | British |
| 13sk.00 | Scottish Gaelic as a second language | White | British |
| 13u..00 | Additional main spoken language | - | - |
| 13u0.00 | Main spoken language Bulgarian | White | Other white |
| 13u1.00 | Main spoken language Romanian | White | Other white |
| 13u2.00 | Main spoken language Oromo | Black | African |
| 13u3.00 | Main spoken language Abkhazian | White | Other white |
| 13u4.00 | Main spoken language Afar | Black | African |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13u5.00 | Main spoken language Afrikaans | - | - |
| 13u6.00 | Main spoken language Armenian | White | Other white |
| 13u7.00 | Main spoken language Assamese | Asian | - |
| 13u8.00 | Main spoken language Aymara | Other | Other |
| 13u9.00 | Main spoken language Azerbaijani | Other | Other |
| 13uA.00 | Main spoken language Bashkir | White | Other white |
| 13uB.00 | Main spoken language Basque | White | Other white |
| 13uC.00 | Main spoken language Dzongkha | Other | Other |
| 13uD.00 | Main spoken language Bihari | - | - |
| 13uE.00 | Main spoken language Bislama | Other | Other |
| 13uF.00 | Main spoken language Breton | White | Other white |
| 13uG.00 | Main spoken language Burmese | Other | Other |
| 13uH.00 | Main spoken language Belarusian | White | Other white |
| 13uJ.00 | Main spoken language Central Khmer | Other | Other |
| 13uK.00 | Main spoken language Catalan | White | Other white |
| 13uL.00 | Main spoken language Slovak | White | Other white |
| 13uM.00 | Main spoken language Corsican | White | Other white |
| 13uN.00 | Main spoken language Danish | White | Other white |
| 13uP.00 | Main spoken language Esperanto | - | - |
| 13uQ.00 | Main spoken language Estonian | White | Other white |
| 13uR.00 | Main spoken language Faeroese | White | Other white |
| 13uS.00 | Main spoken language Fijian | Other | Other |
| 13uT.00 | Main spoken language Finnish | White | Other white |
| 13uV.00 | Main spoken language Frisian | White | Other white |
| 13uW.00 | Main spoken language Galician | White | Other white |
| 13uX.00 | Main spoken language Georgian | White | Other white |
| 13uY.00 | Main spoken language Kalaallisut | Other | Other |
| 13uY.11 | Main spoken language Greenlandic | Other | Other |
| 13uZ.00 | Main spoken language Guarani | Other | Other |
| 13ua.00 | Main spoken language Hungarian | White | Other white |
| 13ub.00 | Main spoken language Icelandic | White | Other white |
| 13uc.00 | Main spoken language Indonesian | Other | Other |
| 13ud.00 | Main spoken language Interlingua | - | - |
| 13ue.00 | Main spoken language Interlingue | - | - |
| 13uf.00 | Main spoken language Inupiaq | Other | Other |
| 13ug.00 | Main spoken language Inuktitut | Other | Other |
| 13uh.00 | Main spoken language Irish | White | Irish |
| 13ui.00 | Main spoken language Javanese | White | Other white |
| 13uj.00 | Main spoken language Kannada | Asian | Indian |
| 13uk.00 | Main spoken language Kashmiri | Asian | - |
| 13ul.00 | Main spoken language Kazakh | Other | Other |
| 13um.00 | Main spoken language Kinyarwanda | Black | African |
| 13un.00 | Main spoken language Kirghiz | Other | Other |
| 13uo.00 | Main spoken language Rundi | Black | African |
| 13up.00 | Main spoken language Lao | Other | Other |
| 13uq.00 | Main spoken language Bamun | Black | African |
| 13uq.11 | Main spoken language Bamoun | Black | African |
| 13ur.00 | Main spoken language Latvian | White | Other white |
| 13us.00 | Main spoken language Macedonian | White | Other white |
| 13ut.00 | Main spoken language Malagasy | Black | African |
| 13uu.00 | Main spoken language Malay | Other | Other |
| 13uv.00 | Main spoken language Maltese | White | Other white |
| 13uw.00 | Main spoken language Maori | Other | Other |
| 13ux.00 | Main spoken language Marathi | Asian | Indian |
| 13uy.00 | Main spoken language Moldavian | White | Other white |
| 13uz.00 | Main spoken language Mongolian | Other | Other |
| 13w..00 | Supplemental main language spoken | - | - |
| 13w0.00 | Main spoken language Nauru | Other | Other |
| 13w1.00 | Main spoken language Nepali | Other | Other |
| 13w2.00 | Main spoken language Occitan | White | Other white |
| 13w3.00 | Main spoken language Oriya | Asian | Indian |
| 13w4.00 | Main spoken language Filipino | Other | Other |
| 13w5.00 | Main spoken language Quechua | Other | Other |
| 13w6.00 | Main spoken language Romansh | White | Other white |
| 13w7.00 | Main spoken language Samoan | Other | Other |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 13w8.00 | Main spoken language Sango | Black | African |
| 13w9.00 | Main spoken language Hindko | Asian | - |
| 13wA.00 | Main spoken language Dari | Other | Other |
| 13wB.00 | Main spoken language Southern Sotho | Black | African |
| 13wC.00 | Main spoken language Tswana | Black | African |
| 13wD.00 | Main spoken language Sindhi | Asian | - |
| 13wE.00 | Main spoken language Ndebele | Black | African |
| 13wF.00 | Main spoken language Swati | Black | African |
| 13wG.00 | Main spoken language Slovenian | White | Other white |
| 13wH.00 | Main spoken language Sundanese | Black | African |
| 13wJ.00 | Main spoken language Tajik | Other | Other |
| 13wK.00 | Main spoken language Tatar | White | Other white |
| 13wL.00 | Main spoken language Telugu | Asian | Indian |
| 13wM.00 | Main spoken language Tibetan | Other | Other |
| 13wN.00 | Main spoken language Tongan | Other | Other |
| 13wP.00 | Main spoken language Tsonga | Black | African |
| 13wQ.00 | Main spoken language Turkmen | Other | Other |
| 13wR.00 | Main spoken language Twi | Black | African |
| 13wS.00 | Main spoken language Uighur | Other | Chinese |
| 13wT.00 | Main spoken language Uzbek | Other | Other |
| 13wV.00 | Main spoken language Tetum | Other | Other |
| 13wW.00 | Main spoken language Wolof | Black | African |
| 13wX.00 | Main spoken language Xhosa | Black | African |
| 13wY.00 | Main spoken language Yiddish | - | - |
| 13wZ.00 | Main spoken language Zhuang | Other | Chinese |
| 13wa.00 | Main spoken language Zulu | Black | African |
| 13wb.00 | Main spoken language Konkani | Asian | Indian |
| 13wc.00 | Main spoken language Aragonese | White | Other white |
| 9NU..00 | Need for interpreter | - | - |
| 9NU0.00 | Interpreter needed | - | - |
| 9NU1.00 | Interpreter not needed | - | - |
| 9NU2.00 | Interpreter needed - Akan | Black | African |
| 9NU3.00 | Interpreter needed - Albanian | White | Other white |
| 9NU4.00 | Interpreter needed - Amharic | Black | African |
| 9NU5.00 | Interpreter needed - Arabic | - | - |
| 9NU6.00 | Interpreter needed - Bengali | Asian | - |
| 9NU7.00 | Interpreter needed - Italian | White | Other white |
| 9NU8.00 | Interpreter needed - Cantonese | Other | Chinese |
| 9NU9.00 | Interpreter needed - Croatian | White | Other white |
| 9NU9.11 | Serbo-Croatian language interpreter needed | White | Other white |
| 9NUA.00 | Interpreter needed - Czech | White | Other white |
| 9NUB.00 | Interpreter needed - Dutch | White | Other white |
| 9NUC.00 | Interpreter needed - Farsi | Other | Other |
| 9NUC.11 | Persian language interpreter needed | Other | Other |
| 9NUD.00 | Interpreter needed - French | - | - |
| 9NUE.00 | Interpreter needed - French Creole | - | - |
| 9NUF.00 | Interpreter needed - Igbo | Black | African |
| 9NUG.00 | Interpreter needed - German | White | Other white |
| 9NUH.00 | Interpreter needed - Greek | White | Other white |
| 9NUJ.00 | Interpreter needed - Gujarati | Asian | - |
| 9NUK.00 | Interpreter needed - Hakka | Other | - |
| 9NUL.00 | Interpreter needed - Hausa | Black | African |
| 9NUM.00 | Interpreter needed - Hebrew | - | - |
| 9NUN.00 | Interpreter needed - Hindi | Asian | - |
| 9NUP.00 | Interpreter needed - Japanese | Other | Other |
| 9NUQ.00 | Interpreter needed - Korean | Other | Other |
| 9NUR.00 | Interpreter needed - Kurdish | Other | Other |
| 9NUS.00 | Interpreter needed - Lingala | Black | African |
| 9NUT.00 | Interpreter needed - Lithuanian | White | Other white |
| 9NUV.00 | Interpreter needed - Ganda | Black | African |
| 9NUW.00 | Interpreter needed - Malayalam | Asian | Indian |
| 9NUX.00 | Interpreter needed - Mandarin | Other | Chinese |
| 9NUY.00 | Interpreter needed - Norwegian | White | Other white |
| 9NUZ.00 | Interpreter needed - Pashto | Other | Other |
| 9NUa.00 | Interpreter needed - Polish | White | Other white |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 9NUb.00 | Interpreter needed - Portuguese | - | - |
| 9NUc.00 | Interpreter needed - Panjabi | Asian | - |
| 9NUc.11 | Punjabi language interpreter needed | Asian | - |
| 9NUd.00 | Interpreter needed - Russian | White | Other white |
| 9NUe.00 | Interpreter needed - Serbian | White | Other white |
| 9NUe.11 | Serbo-Croatian language interpreter needed | White | Other white |
| 9NUf.00 | Interpreter needed - Shona | Black | African |
| 9NUg.00 | Interpreter needed - Sinhala | Asian | Other Asian |
| 9NUh.00 | Interpreter needed - Somali | Black | African |
| 9NUi.00 | Interpreter needed - Spanish | - | - |
| 9NUj.00 | Interpreter needed - Swahili | Black | African |
| 9NUk.00 | Interpreter needed - Swedish | White | Other white |
| 9NUl.00 | Interpreter needed - Sylheti | Asian | - |
| 9NUm.00 | Interpreter needed - Tagalog | Other | Other |
| 9NUn.00 | Interpreter needed - Tamil | Asian | - |
| 9NUo.00 | Interpreter needed - Thai | Other | Other |
| 9NUp.00 | Interpreter needed - Tigrinya | Black | African |
| 9NUq.00 | Interpreter needed - Turkish | White | Other white |
| 9NUr.00 | Interpreter needed - Ukrainian | White | Other white |
| 9NUs.00 | Interpreter needed - Urdu | Asian | - |
| 9NUt.00 | Interpreter needed - Vietnamese | Other | Other |
| 9NUu.00 | Interpreter needed - Welsh | White | British |
| 9NUv.00 | Interpreter needed - Yoruba | Black | African |
| 9NUw.00 | Interpreter needed - British Sign Language | - | - |
| 9NUx.00 | Interpreter needed - Makaton Sign Language | - | - |
| 9NUy.00 | Romanian language interpreter needed | White | Other white |
| 9NUz.00 | Bulgarian language interpreter needed | White | Other white |
| 9Nm..00 | Other interpreter needed | - | - |
| 9Nm0.00 | Mongolian language interpreter needed | Other | Other |
| 9Nm1.00 | Moldavian language interpreter needed | White | Other white |
| 9Nm2.00 | Marathi language interpreter needed | Asian | Indian |
| 9Nm3.00 | Maltese language interpreter needed | White | Other white |
| 9Nm4.00 | Luganda language interpreter needed | Black | African |
| 9Nm5.00 | Ethiopian language interpreter needed | Black | African |
| 9Nm6.00 | Brawa language interpreter needed | - | - |
| 9Nm7.00 | Kirghiz language interpreter needed | Other | Other |
| 9Nm8.00 | Iban language interpreter needed | Other | Other |
| 9Nm9.00 | Maori language interpreter needed | Other | Other |
| 9NmA.00 | Macedonian language interpreter needed | White | Other white |
| 9NmB.00 | Malagasy language interpreter needed | Other | Other |
| 9NmC.00 | Latvian language interpreter needed | White | Other white |
| 9NmD.00 | Kannada language interpreter needed | Asian | Indian |
| 9NmE.00 | Kinyarwanda language interpreter needed | Black | African |
| 9NmF.00 | Malay language interpreter needed | Other | Other |
| 9NmG.00 | Kashmiri language interpreter needed | Asian | - |
| 9NmH.00 | Kazakh language interpreter needed | Other | Other |
| 9NmJ.00 | Inupiaq language interpreter needed | Other | Other |
| 9NmK.00 | Javanese language interpreter needed | Other | Other |
| 9NmL.00 | Inuktitut language interpreter needed | Other | Other |
| 9NmM.00 | Interlingue language interpreter needed | - | - |
| 9NmN.00 | Lao language interpreter needed | Other | Other |
| 9NmP.00 | Icelandic language interpreter needed | White | Other white |
| 9NmQ.00 | Hungarian language interpreter needed | White | Other white |
| 9NmR.00 | Guarani language interpreter needed | Other | Other |
| 9NmS.00 | Georgian language interpreter needed | White | Other white |
| 9NmT.00 | Frisian language interpreter needed | White | Other white |
| 9NmV.00 | Faeroese language interpreter needed | White | Other white |
| 9NmW.00 | Fijian language interpreter needed | Other | Other |
| 9NmX.00 | Galician language interpreter needed | White | Other white |
| 9NmY.00 | Esperanto language interpreter needed | - | - |
| 9NmZ.00 | Estonian language interpreter needed | White | Other white |
| 9Nma.00 | Corsican language interpreter needed | White | Other white |
| 9Nmb.00 | Danish language interpreter needed | White | Other white |
| 9Nmc.00 | Kalaallisut language interpreter needed | Other | Other |
| 9Nmc.11 | Greenlandic language interpreter needed | Other | Other |

**Table G.2** Continued.

| Read code | Code description | 5-category ethnicity group | 16-category ethnicity group |
|---|---|---|---|
| 9Nmd.00 | Catalan language interpreter needed | White | Other white |
| 9Nme.00 | Belarusian language interpreter needed | White | Other white |
| 9Nmf.00 | Indonesian language interpreter needed | Other | Other |
| 9Nmg.00 | Breton language interpreter needed | White | Other white |
| 9Nmh.00 | Bislama language interpreter needed | Other | Other |
| 9Nmi.00 | Bihari language interpreter needed | Asian | - |
| 9Nmj.00 | Assamese language interpreter needed | Asian | - |
| 9Nmk.00 | Armenian language interpreter needed | White | Other white |
| 9Nml.00 | Central Khmer language interpreter needed | Other | Other |
| 9Nmm.00 | Burmese language interpreter needed | Other | Other |
| 9Nmn.00 | Aymara language interpreter needed | Other | Other |
| 9Nmo.00 | Afrikaans language interpreter needed | - | - |
| 9Nmp.00 | Azerbaijani language interpreter needed | Other | Other |
| 9Nmq.00 | Basque language interpreter needed | White | Other white |
| 9Nmr.00 | Afar language interpreter needed | Black | African |
| 9Nms.00 | Abkhazian language interpreter needed | White | Other white |
| 9Nmt.00 | Dzongkha language interpreter needed | Other | Other |
| 9Nmu.00 | Zulu language interpreter needed | Black | African |
| 9Nmv.00 | Zhuang language interpreter needed | Other | Chinese |
| 9Nmw.00 | Uzbek language interpreter needed | Other | Other |
| 9Nmx.00 | Oromo language interpreter needed | Black | African |
| 9Nmy.00 | Yiddish language interpreter needed | - | - |
| 9Nmz.00 | Rundi language interpreter needed | Black | African |
| 9Nn..00 | Further interpreter needed | - | - |
| 9Nn0.00 | Tibetan language interpreter needed | Other | Other |
| 9Nn1.00 | Tsonga language interpreter needed | Black | African |
| 9Nn2.00 | Tatar language interpreter needed | White | Other white |
| 9Nn3.00 | Twi language interpreter needed | Black | African |
| 9Nn4.00 | Telugu language interpreter needed | Asian | Indian |
| 9Nn5.00 | Tongan language interpreter needed | Other | Other |
| 9Nn6.00 | Turkmen language interpreter needed | Other | Other |
| 9Nn7.00 | Slovenian language interpreter needed | White | Other white |
| 9Nn8.00 | Swati language interpreter needed | Black | African |
| 9Nn9.00 | Southern Sotho language interpreter needed | Black | African |
| 9NnA.00 | Tajik language interpreter needed | Other | Other |
| 9NnB.00 | Sindhi language interpreter needed | Asian | - |
| 9NnC.00 | Sundanese language interpreter needed | Black | African |
| 9NnD.00 | Samoan language interpreter needed | Other | Other |
| 9NnE.00 | Tswana language interpreter needed | Black | African |
| 9NnF.00 | Quechua language interpreter needed | Other | Other |
| 9NnG.00 | Sango language interpreter needed | Black | African |
| 9NnH.00 | Uighur language interpreter needed | Other | - |
| 9NnJ.00 | Oriya language interpreter needed | Asian | Indian |
| 9NnK.00 | Nepali language interpreter needed | Other | Other |
| 9NnL.00 | Occitan language interpreter needed | White | Other white |
| 9NnM.00 | Nauru language interpreter needed | Other | Other |
| 9NnN.00 | Romansh language interpreter needed | White | Other white |
| 9NnP.00 | Xhosa language interpreter needed | Black | African |

Abbreviations: ONS, Office for National Statistics; White & Caribb., White and Black Caribbean; White & African, White and Black African.

**Table G.3** Read codes related to pregnancy or delivery, grouped into categories.

| Read code | Code description | Category |
|---|---|---|
| 13H8.00 | Illegitimate pregnancy | Pregnant |
| 13Hd.00 | Teenage pregnancy | Pregnant |
| 13If000 | Unborn child is cause for safeguarding concern | Pregnant |
| 13S..00 | Pregnancy benefits | Pregnant |
| 13SZ.00 | Pregnancy benefit NOS | Pregnant |
| 615C.00 | IUD failure - pregnant | Pregnant |
| 615C.11 | Pregnant, IUD failure | Pregnant |
| 6166.00 | Pregnant, diaphragm failure | Pregnant |
| 6174.00 | Pregnant, sheath failure | Pregnant |
| 62...00 | Patient pregnant | Pregnant |
| 621..00 | Patient currently pregnant | Pregnant |
| 621..11 | Pregnancy confirmed | Pregnant |
| 6213.00 | Pregnant - V.E. confirms | Pregnant |
| 6214.00 | Pregnant - on history | Pregnant |
| 6215.00 | Pregnant - on abdom. palpation | Pregnant |
| 6216.00 | Pregnant - planned | Pregnant |
| 6217.00 | Pregnant - unplanned - wanted | Pregnant |
| 621A.00 | Pregnancy unplanned ? wanted | Pregnant |
| 621B.00 | Pregnant - ? planned | Pregnant |
| 621C.00 | Unplanned pregnancy | Pregnant |
| 621D.00 | Concealed pregnancy | Pregnant |
| 621Z.00 | Patient pregnant NOS | Pregnant |
| 62O7.00 | Pregnancy prolonged - 41 weeks | Pregnant |
| 62O8.00 | Pregnancy prolonged - 42 weeks | Pregnant |
| 8B68.00 | Pregnancy prophylactic therapy | Pregnant |
| 8B7..11 | Pregnancy vitamin/iron prophyl | Pregnant |
| 8B74.00 | Iron supplement in pregnancy | Pregnant |
| 8B75.00 | Vitamin supplement - pregnancy | Pregnant |
| L13..00 | Excessive pregnancy vomiting | Pregnant |
| L13..12 | Hyperemesis of pregnancy | Pregnant |
| L132.00 | Late vomiting of pregnancy | Pregnant |
| L132000 | Late pregnancy vomiting unspecified | Pregnant |
| L132100 | Late pregnancy vomiting - delivered | Pregnant |
| L132200 | Late pregnancy vomiting - not delivered | Pregnant |
| L132z00 | Late pregnancy vomiting NOS | Pregnant |
| L13y.00 | Other pregnancy vomiting | Pregnant |
| L13y000 | Other pregnancy vomiting unspecified | Pregnant |
| L13y100 | Other pregnancy vomiting - delivered | Pregnant |
| L13y200 | Other pregnancy vomiting - not delivered | Pregnant |
| L13yz00 | Other pregnancy vomiting NOS | Pregnant |
| L13z.00 | Unspecified pregnancy vomiting | Pregnant |
| L13z000 | Unspecified pregnancy vomiting unspecified | Pregnant |
| L13z100 | Unspecified pregnancy vomiting - delivered | Pregnant |
| L13z200 | Unspecified pregnancy vomiting - not delivered | Pregnant |
| L13zz00 | Unspecified pregnancy vomiting NOS | Pregnant |
| L161.00 | Oedema or excessive weight gain in pregnancy no hypertension | Pregnant |
| L161.11 | Excessive weight gain in pregnancy | Pregnant |
| L161000 | Oedema or excessive weight gain in pregnancy, unspecified | Pregnant |
| L161100 | Oedema or excessive weight gain in pregnancy, delivered | Pregnant |
| L161300 | Oedema or excessive weight gain in pregnancy - not delivered | Pregnant |
| L161z00 | Oedema or excessive weight gain in pregnancy NOS | Pregnant |
| L168.00 | Fatigue during pregnancy | Pregnant |
| L168000 | Fatigue during pregnancy unspecified | Pregnant |
| L168100 | Fatigue during pregnancy - delivered | Pregnant |
| L168200 | Fatigue during pregnancy - delivered with postnatal comp | Pregnant |
| L168300 | Fatigue during pregnancy - not delivered | Pregnant |
| L168400 | Fatigue during pregnancy with postnatal complication | Pregnant |
| L168z00 | Fatigue during pregnancy NOS | Pregnant |
| L16D.00 | Excessive weight gain in pregnancy | Pregnant |
| L16E.00 | Pregnancy pruritus | Pregnant |
| L2...00 | Risk factors in pregnancy | Pregnant |
| L21..00 | Multiple pregnancy | Pregnant |
| L210.00 | Twin pregnancy | Pregnant |
| L210000 | Twin pregnancy unspecified | Pregnant |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| L210200 | Twin pregnancy with antenatal problem | Pregnant |
| L210z00 | Twin pregnancy NOS | Pregnant |
| L211.00 | Triplet pregnancy | Pregnant |
| L211000 | Triplet pregnancy unspecified | Pregnant |
| L211200 | Triplet pregnancy with antenatal problem | Pregnant |
| L211z00 | Triplet pregnancy NOS | Pregnant |
| L212.00 | Quadruplet pregnancy | Pregnant |
| L212000 | Quadruplet pregnancy unspecified | Pregnant |
| L212200 | Quadruplet pregnancy with antenatal problem | Pregnant |
| L212z00 | Quadruplet pregnancy NOS | Pregnant |
| L21y.00 | Other multiple pregnancy | Pregnant |
| L21y000 | Other multiple pregnancy unspecified | Pregnant |
| L21y200 | Other multiple pregnancy with antenatal problem | Pregnant |
| L21yz00 | Other multiple pregnancy NOS | Pregnant |
| L21z.00 | Multiple pregnancy NOS | Pregnant |
| L21z000 | Multiple pregnancy NOS, unspecified | Pregnant |
| L21z200 | Multiple pregnancy NOS with antenatal problem | Pregnant |
| L21zz00 | Multiple pregnancy NOS | Pregnant |
| L222000 | Breech presentation unspecified | Pregnant |
| L228.00 | Multiple pregnancy with malpresentation | Pregnant |
| L228000 | Multiple pregnancy with malpresentation unspecified | Pregnant |
| L228z00 | Multiple pregnancy with malpresentation NOS | Pregnant |
| L22y.00 | Other fetal malposition and malpresentation | Pregnant |
| L22y000 | Other fetal malposition and malpresentation unspecified | Pregnant |
| L22y200 | Other fetal malposition and malpresentation with a/n prob | Pregnant |
| L22yz00 | Other fetal malposition and malpresentation NOS | Pregnant |
| L22z.00 | Fetal malposition and malpresentation NOS | Pregnant |
| L22z000 | Fetal malposition and malpresentation NOS, unspecified | Pregnant |
| L22z200 | Fetal malposition and malpresentation NOS with a/n problem | Pregnant |
| L22zz00 | Fetal malposition and malpresentation NOS | Pregnant |
| L265.00 | Small-for-dates fetus in pregnancy | Pregnant |
| L266.00 | Large-for-dates fetus in pregnancy | Pregnant |
| L2B..00 | Low weight gain in pregnancy | Pregnant |
| L2C..00 | Malnutrition in pregnancy | Pregnant |
| L2y..00 | Other specified risk factors in pregnancy | Pregnant |
| L2z..00 | Risk factors in pregnancy NOS | Pregnant |
| Z2...00 | Pregnancy, childbirth and puerperium observations | Pregnant |
| Z22..00 | Pregnancy observations | Pregnant |
| Z225.00 | Normal pregnancy | Pregnant |
| Z226.00 | Pregnancy problem | Pregnant |
| Z227.00 | Confirmation of pregnancy | Pregnant |
| Z229.00 | Observation of position of pregnancy | Pregnant |
| Z229100 | Intrauterine pregnancy | Pregnant |
| Z22A.00 | Observation of pattern of pregnancy | Pregnant |
| Z22A100 | Low risk pregnancy | Pregnant |
| Z22A200 | High risk pregnancy | Pregnant |
| Z22A211 | HRP - High risk pregnancy | Pregnant |
| Z22A300 | Concealed pregnancy | Pregnant |
| Z22A400 | Early stage of pregnancy | Pregnant |
| Z22A500 | Biochemical pregnancy | Pregnant |
| Z22A600 | Teenage pregnancy | Pregnant |
| Z22A800 | Undiagnosed pregnancy | Pregnant |
| Z22AA00 | Wanted pregnancy | Pregnant |
| Z22AB00 | Unplanned pregnancy | Pregnant |
| Z22AB11 | Accidental pregnancy | Pregnant |
| Z22AC00 | Pregnancy with uncertain dates | Pregnant |
| Z22AD00 | Presentation of pregnancy | Pregnant |
| Z22AD11 | Reported conception - pregnancy | Pregnant |
| Z22B.00 | Observation of quantity of pregnancy | Pregnant |
| Z22B100 | Single pregnancy | Pregnant |
| Z22B500 | Quintuplet pregnancy | Pregnant |
| Z22B600 | Sextuplet pregnancy | Pregnant |
| Z22B700 | Septulet pregnancy | Pregnant |
| Z22B800 | Undiagnosed multiple pregnancy | Pregnant |
| Z22B900 | Continuing pregnancy after abortion of sibling fetus | Pregnant |
| Z22BA00 | Contin pregnancy after intrauterine death of sibling fetus | Pregnant |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| Z22C311 | Pregnancy duration | Pregnant |
| Z22C313 | Duration of pregnancy | Pregnant |
| Z22C314 | Weeks pregnant | Pregnant |
| Z22D100 | Viable pregnancy | Pregnant |
| ZV22.00 | [V]Normal pregnancy | Pregnant |
| ZV22.11 | [V]Supervision of normal pregnancy | Pregnant |
| ZV22000 | [V]First normal pregnancy supervision | Pregnant |
| ZV22100 | [V]Other normal pregnancy supervision | Pregnant |
| ZV22200 | [V]Pregnancy confirmed | Pregnant |
| ZV22300 | [V]Pregnant state, incidental | Pregnant |
| ZV22400 | [V]Supervision of other normal pregnancy | Pregnant |
| ZV22y00 | [V]Other specified pregnant state | Pregnant |
| ZV22z00 | [V]Unspecified pregnant state | Pregnant |
| ZV23.00 | [V]High-risk pregnancy supervision | Pregnant |
| ZV23000 | [V]Pregnancy with history of infertility | Pregnant |
| ZV23400 | [V]Pregnancy with other poor obstetric history | Pregnant |
| ZV23500 | [V]Pregnancy with other poor reproductive history | Pregnant |
| ZV23600 | [V]Supervisn/pregnancy wth history insufficnt antenatal care | Pregnant |
| ZV23800 | [V]Supervision of high-risk pregnancy due to social problems | Pregnant |
| ZV23y00 | [V]Other specified high-risk pregnancy | Pregnant |
| ZV23z00 | [V]Unspecified high-risk pregnancy | Pregnant |
| ZVu2300 | [X]Supervision of other normal pregnancy | Pregnant |
| ZVu2500 | [X]Supervision of other high-risk pregnancies | Pregnant |
| 4453.00 | Serum pregnancy test positive | Pregnancy Test |
| 4654.00 | Urine pregnancy test positive | Pregnancy Test |
| 6211.00 | Pregnant - urine test confirms | Pregnancy Test |
| 6212.00 | Pregnant - blood test confirms | Pregnancy Test |
| 584..11 | Fetal U-S scan | Antenatal ultrasound scan |
| 5845.00 | U-S scan - fetal cephalometry | Antenatal ultrasound scan |
| 5846.00 | U-S scan - fetal maturity | Antenatal ultrasound scan |
| 5849.00 | U-S scan - fetal presentation | Antenatal ultrasound scan |
| 584C.00 | Antenatal ultrasound result received | Antenatal ultrasound scan |
| 584D.00 | Antenatal ultrasound confirms intra-uterine pregnancy | Antenatal ultrasound scan |
| 62G..00 | Antenatal ultrasound scan | Antenatal ultrasound scan |
| 62G6.00 | A/N U/S scan normal += dates | Antenatal ultrasound scan |
| 62G7.00 | A/N U/S scan normal +? dates | Antenatal ultrasound scan |
| 62GB.00 | Antenatal ultrasounds scan at 4-8 weeks | Antenatal ultrasound scan |
| 62GC.00 | Antenatal ultrasound scan at 9-16 weeks | Antenatal ultrasound scan |
| 62GD.00 | Antenatal ultrasound scan at 17-22 weeks | Antenatal ultrasound scan |
| 62GE.00 | Antenatal ultrasound scan at 22-40 weeks | Antenatal ultrasound scan |
| 62GZ.00 | Antenatal ultrasound scan NOS | Antenatal ultrasound scan |
| 7F27.00 | Non routine obstetric scan for fetal observations | Antenatal ultrasound scan |
| 7F27200 | Fetal biometry | Antenatal ultrasound scan |
| 7F27y00 | OS non routine obstetric scan for fetal observations | Antenatal ultrasound scan |
| 7F27z00 | Non routine obstetric scan for fetal observations NOS | Antenatal ultrasound scan |
| 7F2B100 | Ultrasound monitoring of early pregnancy | Antenatal ultrasound scan |
| 272..00 | O/E - fetal presentation | Antenatal examination |
| 2726.00 | O/E -fetal presentation unsure | Antenatal examination |
| 272Z.00 | O/E - fetal presentation NOS | Antenatal examination |
| 274Z.00 | O/E - fetal station NOS | Antenatal examination |
| 275..00 | O/E - fetal movements | Antenatal examination |
| 2751.00 | O/E - no fetal movements | Antenatal examination |
| 2752.00 | O/E - fetal movements seen | Antenatal examination |
| 2753.00 | O/E - fetal movements felt | Antenatal examination |
| 2755.00 | O/E - fetal movemnt.diminished | Antenatal examination |
| 275Z.00 | O/E - fetal movements NOS | Antenatal examination |
| 276..00 | O/E - fetal heart heard | Antenatal examination |
| 2764.00 | O/E - fetal heart 80-100 | Antenatal examination |
| 2765.00 | O/E - fetal heart 100-120 | Antenatal examination |
| 2766.00 | O/E - fetal heart 120-160 | Antenatal examination |
| 2767.00 | O/E - fetal heart 160-180 | Antenatal examination |
| 2768.00 | O/E - fetal heart 180-200 | Antenatal examination |
| 2769.00 | O/E - fetal heart > 200 | Antenatal examination |
| 276A.00 | O/E - fetal heart -type 1 dips | Antenatal examination |
| 276B.00 | O/E - fetal heart -type 2 dips | Antenatal examination |
| 276Z.00 | O/E - fetal heart NOS | Antenatal examination |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 62N..00 | Antenatal examinations | Antenatal examination |
| 62N1.00 | A/N booking examination | Antenatal examination |
| 62N2.00 | A/N 12 weeks examination | Antenatal examination |
| 62N3.00 | A/N 16 week examination | Antenatal examination |
| 62N4.00 | A/N 20 week examination | Antenatal examination |
| 62N5.00 | A/N 24 week examination | Antenatal examination |
| 62N6.00 | A/N 28 week examination | Antenatal examination |
| 62N7.00 | A/N 30 week examination | Antenatal examination |
| 62N8.00 | A/N 32 week examination | Antenatal examination |
| 62N9.00 | A/N 34 week examination | Antenatal examination |
| 62NA.00 | A/N 35 week examination | Antenatal examination |
| 62NB.00 | A/N 36 week examination | Antenatal examination |
| 62NC.00 | A/N 37 week examination | Antenatal examination |
| 62ND.00 | A/N 38 week examination | Antenatal examination |
| 62NE.00 | A/N 39 week examination | Antenatal examination |
| 62NF.00 | A/N 40 week examination | Antenatal examination |
| 62NG.00 | A/N 41 week examination | Antenatal examination |
| 62NH.00 | A/N 42 week examination | Antenatal examination |
| 62NJ.00 | Antenatal 22 week examination | Antenatal examination |
| 62NK.00 | Antenatal 25 week examination | Antenatal examination |
| 62NL.00 | Antenatal 31 week examination | Antenatal examination |
| 62NZ.00 | Antenatal examination NOS | Antenatal examination |
| 62O1.00 | Fetal movements felt | Antenatal examination |
| 62O2.00 | Fetal movements seen | Antenatal examination |
| Z235.00 | Observation of shape of pregnant abdomen | Antenatal examination |
| Z235100 | Ovoid pregnant abdomen | Antenatal examination |
| Z235200 | Rounded pregnant abdomen | Antenatal examination |
| Z235211 | Globular pregnant abdomen | Antenatal examination |
| Z235300 | Transversely enlarged pregnant abdomen | Antenatal examination |
| Z235400 | Pendulous pregnant abdomen | Antenatal examination |
| Z236300 | Pregnant uterus displaced laterally | Antenatal examination |
| Z23D100 | Girth of pregnant abdomen | Antenatal examination |
| Z23D200 | Pregnant abdomen observation | Antenatal examination |
| 38B6.00 | Antenatal risk assessment | Antenatal care |
| 62...11 | Antenatal care | Antenatal care |
| 62...13 | Pregnancy care | Antenatal care |
| 622..00 | Antenatal care: gravida No. | Antenatal care |
| 6221.00 | Antenatal care: primigravida | Antenatal care |
| 6222.00 | Antenatal care: 2nd pregnancy | Antenatal care |
| 6223.00 | Antenatal care: 3rd pregnancy | Antenatal care |
| 6224.00 | Antenatal care: multip | Antenatal care |
| 622Z.00 | Antenatal care: gravida NOS | Antenatal care |
| 623..00 | A/N care: obstetric risk | Antenatal care |
| 6231.00 | A/N care: uncertain dates | Antenatal care |
| 6233.00 | A/N care: grand multip | Antenatal care |
| 6236.00 | A/N care: poor obstetr history | Antenatal care |
| 623Z.00 | A/N care: obstetric risk NOS | Antenatal care |
| 624..00 | A/N care: precious pregnancy | Antenatal care |
| 6241.00 | A/N care: elderly primip. | Antenatal care |
| 624Z.00 | A/N care: precious preg. NOS | Antenatal care |
| 625..00 | A/N care: social risk | Antenatal care |
| 6251.00 | A/N care: poor home conditions | Antenatal care |
| 6252.00 | A/N care: poor A/N attender | Antenatal care |
| 6253.00 | A/N care: late booker | Antenatal care |
| 625Z.00 | A/N care: social risk NOS | Antenatal care |
| 626..00 | A/N care: medical risk | Antenatal care |
| 627..00 | A/N care: gynae. risk | Antenatal care |
| 628..00 | A/N care: risk NOS | Antenatal care |
| 6281.00 | A/N care: under 5ft tall | Antenatal care |
| 6282.00 | A/N care:10yrs+since last preg | Antenatal care |
| 6283.00 | A/N care: primip. < 17 years | Antenatal care |
| 6284.00 | A/N care: primip. > 30 years | Antenatal care |
| 6285.00 | A/N care: multip. > 35 years | Antenatal care |
| 628Z.00 | A/N risk NOS | Antenatal care |
| 62A..00 | A/N care provider | Antenatal care |
| 62A1.00 | A/N care from G.P. | Antenatal care |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 62A2.00 | A/N care from consultant | Antenatal care |
| 62A3.00 | A/N - shared care | Antenatal care |
| 62A4.00 | A/N care midwifery led | Antenatal care |
| 62AZ.00 | A/N care provider NOS | Antenatal care |
| 62O..00 | Misc. antenatal data | Antenatal care |
| 62O..11 | Fetal maturity - A/N | Antenatal care |
| 62O3.00 | Fetal maturity: dates = size | Antenatal care |
| 62O4.00 | Fetal maturity: dates not=size | Antenatal care |
| 62OZ.00 | Misc. antenatal data NOS | Antenatal care |
| 62Y..00 | Routine antenatal care | Antenatal care |
| 62a..00 | Pregnancy review | Antenatal care |
| 62a..11 | Review of pregnancy | Antenatal care |
| 6B22.00 | Sure Start antenatal visit | Antenatal care |
| 8HT9.00 | Referral to antenatal clinic | Antenatal care |
| 9N1N.00 | Seen in antenatal clinic | Antenatal care |
| 9NFV.00 | Health visitor antenatal visit | Antenatal care |
| 9NV1.00 | Antenatal clinic | Antenatal care |
| 9Nil.00 | Did not attend antenatal appointment | Antenatal care |
| L263800 | Maternal care for fetal decelerations during pregnancy | Antenatal care |
| L263900 | Maternal care for fetal tachycardia during pregnancy | Antenatal care |
| L263A00 | Maternal care for fetal bradycardia during pregnancy | Antenatal care |
| L263A11 | Maternal care for reduced fetal heart rate during pregnancy | Antenatal care |
| L263B00 | Maternal care for fetal acidosis during pregnancy | Antenatal care |
| Z212.00 | Antenatal care | Antenatal care |
| Z212.11 | Pregnancy care | Antenatal care |
| 62I..11 | AFP test - antenatal | Antenatal screening or test |
| 62K..00 | Antenatal syphilis screen | Antenatal screening or test |
| 62KZ.00 | Antenatal syphilis screen NOS | Antenatal screening or test |
| 62L..00 | Antenatal blood group screen | Antenatal screening or test |
| 62M..00 | Antenatal sickle cell screen | Antenatal screening or test |
| 62W..00 | Antenatal blood tests | Antenatal screening or test |
| 62b..00 | Antenatal HIV screening | Antenatal screening or test |
| 62c..00 | Antenatal screening | Antenatal screening or test |
| 65QG.00 | Antenatal screening shows non sig haemoglobinopathy carrier | Antenatal screening or test |
| 68b..00 | Antenatal screening status | Antenatal screening or test |
| 68b6.00 | Antenatal screening declined | Antenatal screening or test |
| ZV28.00 | [V]Antenatal screening | Antenatal screening or test |
| ZV28600 | [V]Antenatal screening for chromosomal anomalies | Antenatal screening or test |
| ZV28y00 | [V]Other specified antenatal screening | Antenatal screening or test |
| ZV28z00 | [V]Unspecified antenatal screening | Antenatal screening or test |
| ZVu2900 | [X]Other antenatal screening | Antenatal screening or test |
| 62B1.00 | Delivery: no place booked | Delivery booking |
| 62B2.00 | Home delivery booked | Delivery booking |
| 62B3.00 | G.P. unit delivery booking | Delivery booking |
| 62B5.00 | Private home delivery booking | Delivery booking |
| 62B6.00 | Delivery booking place changed | Delivery booking |
| 62B8.00 | Midwife unit delivery booking | Delivery booking |
| 62BZ.00 | Delivery booking - place NOS | Delivery booking |
| 62C1.00 | Short stay delivery booking | Delivery booking |
| 62C2.00 | Full stay delivery booking | Delivery booking |
| 62CZ.00 | Delivery booking - stay NOS | Delivery booking |
| 62V..00 | Delivery place planned | Delivery booking |
| 62V0.00 | Home delivery planned | Delivery booking |
| Z212100 | Delivery place planned | Delivery booking |
| Z212200 | Home delivery planned | Delivery booking |
| Z212300 | Delivery place booked | Delivery booking |
| 1514.12 | Estimated date of delivery | Estimated delivery date |
| 1514000 | Estimated date of delivery from last period | Estimated delivery date |
| 1514100 | Estimated date of delivery by antenatal ultrasound scan | Estimated delivery date |
| Z22C100 | Estimated date of delivery from last period | Estimated delivery date |
| Z22C200 | Estimated date of delivery from last normal period | Estimated delivery date |
| 62F..00 | Antenatal amniocentesis | Amniocentesis |
| 62F6.00 | A/N amniocentesis - normal | Amniocentesis |
| 62FZ.00 | Antenatal amniocentesis NOS | Amniocentesis |
| ZVu2600 | [X]Other antenatal screening based on amniocentesis | Amniocentesis |
| 63...00 | Birth details | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 631..00 | Place of birth | Birth or delivery |
| 631..11 | Born - place delivered | Birth or delivery |
| 6311.00 | Home birth | Birth or delivery |
| 6312.00 | GP unit birth | Birth or delivery |
| 6313.00 | Consultant unit birth | Birth or delivery |
| 6314.00 | Nursing home birth | Birth or delivery |
| 6315.00 | Ambulance birth | Birth or delivery |
| 6316.00 | Born before arrival | Birth or delivery |
| 6317.00 | Born in transit to hospital | Birth or delivery |
| 6318.00 | Born in hospital | Birth or delivery |
| 631Z.00 | Place of birth NOS | Birth or delivery |
| 633..00 | Outcome of delivery | Birth or delivery |
| 633..11 | Livebirth | Birth or delivery |
| 633..13 | Triplet birth | Birth or delivery |
| 633..14 | Twin birth | Birth or delivery |
| 6331.00 | Single live birth | Birth or delivery |
| 6333.00 | Twins - both live born | Birth or delivery |
| 6334.00 | Twins - 1 still + 1 live born | Birth or delivery |
| 6336.00 | Triplets - all live born | Birth or delivery |
| 6337.00 | Triplets -2 live+ 1 still born | Birth or delivery |
| 6338.00 | Triplets-1 live+ 2 still born | Birth or delivery |
| 633D.00 | Order of birth at delivery | Birth or delivery |
| 633Z.00 | Outcome of delivery NOS | Birth or delivery |
| 633a.00 | Birth of child | Birth or delivery |
| 63CL.00 | One of multiple birth | Birth or delivery |
| 63D7.00 | Complete placenta at delivery | Birth or delivery |
| 63E..00 | Labour details | Birth or delivery |
| 63E1.00 | Spontaneous onset of labour | Birth or delivery |
| 63E2.00 | Normal birth | Birth or delivery |
| 63E3.00 | Normal labour | Birth or delivery |
| 63F..00 | Birth details not known | Birth or delivery |
| 63G..00 | Uterine membrane observations | Birth or delivery |
| 63G0.00 | Membranes complete | Birth or delivery |
| 63G1.00 | Membranes incomplete | Birth or delivery |
| 63H..00 | Time of delivery | Birth or delivery |
| 63Z..00 | Birth details NOS | Birth or delivery |
| 7F...11 | Childbirth operations | Birth or delivery |
| 7F...12 | Pregnancy operations | Birth or delivery |
| 7F...13 | Puerperium operations | Birth or delivery |
| 7F06012 | Shirodkar suture in pregnancy | Birth or delivery |
| 7F1..00 | Induction and delivery operations | Birth or delivery |
| 7F1..11 | Labour operations | Birth or delivery |
| 7F10.00 | Surgical induction of labour | Birth or delivery |
| 7F10y00 | Other specified surgical induction of labour | Birth or delivery |
| 7F10z00 | Surgical induction of labour NOS | Birth or delivery |
| 7F11.00 | Other induction of labour | Birth or delivery |
| 7F11000 | Oxytocic induction of labour | Birth or delivery |
| 7F11100 | Induction of labour using prostaglandins | Birth or delivery |
| 7F11200 | Syntocinon induction of labour | Birth or delivery |
| 7F11300 | Medical induction of labour | Birth or delivery |
| 7F11y00 | Other specified other induction of labour | Birth or delivery |
| 7F11z00 | Other induction of labour NOS | Birth or delivery |
| 7F12.00 | Elective caesarean delivery | Birth or delivery |
| 7F12000 | Elective upper uterine segment caesarean delivery | Birth or delivery |
| 7F12100 | Elective lower uterine segment caesarean delivery | Birth or delivery |
| 7F12111 | Elective lower uterine segment caesarean section (LSCS) | Birth or delivery |
| 7F12y00 | Other specified elective caesarean delivery | Birth or delivery |
| 7F12z00 | Elective caesarean delivery NOS | Birth or delivery |
| 7F13.00 | Other caesarean delivery | Birth or delivery |
| 7F13000 | Upper uterine segment caesarean delivery NEC | Birth or delivery |
| 7F13100 | Lower uterine segment caesarean delivery NEC | Birth or delivery |
| 7F13111 | Lower uterine segment caesarean section (LSCS) NEC | Birth or delivery |
| 7F13200 | Extraperitoneal caesarean section | Birth or delivery |
| 7F13300 | Emergency caesarean section | Birth or delivery |
| 7F13y00 | Other specified other caesarean delivery | Birth or delivery |
| 7F13z00 | Other caesarean delivery NOS | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 7F14.00 | Breech extraction delivery | Birth or delivery |
| 7F14000 | Breech extraction delivery with version | Birth or delivery |
| 7F14100 | Forceps to aftercoming head (breech) | Birth or delivery |
| 7F14y00 | Other specified breech extraction delivery | Birth or delivery |
| 7F14z00 | Breech extraction delivery NOS | Birth or delivery |
| 7F15.00 | Other breech delivery | Birth or delivery |
| 7F15000 | Spontaneous breech delivery | Birth or delivery |
| 7F15100 | Assisted breech delivery | Birth or delivery |
| 7F15y00 | Other specified other breech delivery | Birth or delivery |
| 7F15z00 | Other breech delivery NOS | Birth or delivery |
| 7F16.00 | Forceps cephalic delivery | Birth or delivery |
| 7F16000 | High forceps cephalic delivery with rotation | Birth or delivery |
| 7F16100 | High forceps cephalic delivery NEC | Birth or delivery |
| 7F16200 | Mid forceps cephalic delivery with rotation | Birth or delivery |
| 7F16300 | Mid forceps cephalic delivery NEC | Birth or delivery |
| 7F16400 | Low forceps cephalic delivery | Birth or delivery |
| 7F16500 | Trial of forceps delivery | Birth or delivery |
| 7F16600 | Failed forceps delivery | Birth or delivery |
| 7F16700 | Barton forceps cephalic delivery with rotation | Birth or delivery |
| 7F16800 | Dehee forceps cephalic delivery with rotation | Birth or delivery |
| 7F16900 | Kielland forceps cephalic delivery with rotation | Birth or delivery |
| 7F16A00 | Scanzoni forceps cephalic delivery with rotation | Birth or delivery |
| 7F16B00 | Piper forceps delivery | Birth or delivery |
| 7F16y00 | Other specified forceps cephalic delivery | Birth or delivery |
| 7F16z00 | Forceps cephalic delivery NOS | Birth or delivery |
| 7F17.00 | Vacuum delivery | Birth or delivery |
| 7F17.11 | Ventouse delivery | Birth or delivery |
| 7F17.12 | Ventouse extraction | Birth or delivery |
| 7F17000 | High vacuum delivery | Birth or delivery |
| 7F17100 | Low vacuum delivery | Birth or delivery |
| 7F17200 | Vacuum delivery before full dilation of cervix | Birth or delivery |
| 7F17300 | Trial of vacuum delivery | Birth or delivery |
| 7F17y00 | Other specified vacuum delivery | Birth or delivery |
| 7F17z00 | Vacuum delivery NOS | Birth or delivery |
| 7F18.00 | Cephalic vaginal deliv abnorm presentation head - no instrum | Birth or delivery |
| 7F18000 | Manip cephalic vaginal deliv abnorm pres head without instrm | Birth or delivery |
| 7F18100 | Nonmanip cephal vagin deliv abnorm pres head without instrum | Birth or delivery |
| 7F18y00 | Cephalic vagin deliv abnorm pres head without instrument OS | Birth or delivery |
| 7F18z00 | Cephalic vagin deliv abnorm pres head without instrument NOS | Birth or delivery |
| 7F19.00 | Normal delivery | Birth or delivery |
| 7F19000 | Manually assisted vaginal delivery | Birth or delivery |
| 7F19100 | Water birth delivery | Birth or delivery |
| 7F19y00 | Other specified normal delivery | Birth or delivery |
| 7F19z00 | Normal delivery NOS | Birth or delivery |
| 7F1A.00 | Other methods of delivery | Birth or delivery |
| 7F1A000 | Caesarean hysterectomy | Birth or delivery |
| 7F1A400 | Trial of labour NEC | Birth or delivery |
| 7F1Ay00 | Other specified other method of delivery | Birth or delivery |
| 7F1Az00 | Other method of delivery NOS | Birth or delivery |
| 7F1B.00 | Other operations to facilitate delivery | Birth or delivery |
| 7F1B000 | Episiotomy to facilitate delivery | Birth or delivery |
| 7F1B100 | Symphysiotomy to facilitate delivery | Birth or delivery |
| 7F1B200 | Pubiotomy to facilitate delivery | Birth or delivery |
| 7F1B400 | Incision of cervix to facilitate delivery | Birth or delivery |
| 7F1By00 | Other specified other operation to facilitate delivery | Birth or delivery |
| 7F1Bz00 | Other operation to facilitate delivery NOS | Birth or delivery |
| 7F1y.00 | Other specified induction or delivery operations | Birth or delivery |
| 7F1z.00 | Induction and delivery operations NOS | Birth or delivery |
| 7F25.11 | Fetal monitoring | Birth or delivery |
| 7F25.13 | Monitoring during labour | Birth or delivery |
| 7F25000 | Fetal heart monitoring NEC | Birth or delivery |
| 7F25100 | Fetal heart monitoring in labour | Birth or delivery |
| 7Fy..00 | Other specified obstetric operations | Birth or delivery |
| 7Fz..00 | Obstetric operations NOS | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 7L16000 | Intravenous induction of labour | Birth or delivery |
| 7M35000 | Gas and air analgesia in labour | Birth or delivery |
| 7M35011 | Entonox analgesia in labour | Birth or delivery |
| 8HE7.00 | Discharged from hospital within 6 hours of delivery | Birth or delivery |
| L030000 | Delivery of viable fetus in abdominal pregnancy | Birth or delivery |
| L142.00 | Early onset of delivery | Birth or delivery |
| L142.11 | Premature delivery | Birth or delivery |
| L142000 | Early onset of delivery unspecified | Birth or delivery |
| L142100 | Early onset of delivery - delivered | Birth or delivery |
| L142z00 | Early onset of delivery NOS | Birth or delivery |
| L143.00 | Premature labour and delivery | Birth or delivery |
| L143100 | Premature labour with premature delivery | Birth or delivery |
| L143200 | Premature labour with term delivery | Birth or delivery |
| L143300 | Premature delivery without labour | Birth or delivery |
| L15..00 | Prolonged or post-term pregnancy | Birth or delivery |
| L15..11 | Post-term pregnancy | Birth or delivery |
| L150.00 | Post-term pregnancy | Birth or delivery |
| L150000 | Post-term pregnancy unspecified | Birth or delivery |
| L150100 | Post-term pregnancy - delivered | Birth or delivery |
| L150200 | Post-term pregnancy - not delivered | Birth or delivery |
| L150z00 | Post-term pregnancy NOS | Birth or delivery |
| L15z.00 | Prolonged pregnancy NOS | Birth or delivery |
| L20..00 | Normal delivery in a completely normal case | Birth or delivery |
| L20..11 | Spontaneous vaginal delivery | Birth or delivery |
| L200.00 | Normal delivery but ante- or post- natal conditions present | Birth or delivery |
| L20z.00 | Normal delivery in completely normal case NOS | Birth or delivery |
| L210100 | Twin pregnancy - delivered | Birth or delivery |
| L211100 | Triplet pregnancy - delivered | Birth or delivery |
| L212100 | Quadruplet pregnancy - delivered | Birth or delivery |
| L213.00 | Multiple delivery | Birth or delivery |
| L213000 | Multiple delivery, all spontaneous | Birth or delivery |
| L213100 | Multiple delivery, all by forceps and vacuum extractor | Birth or delivery |
| L213200 | Multiple delivery, all by caesarean section | Birth or delivery |
| L21y100 | Other multiple pregnancy - delivered | Birth or delivery |
| L21z100 | Multiple pregnancy NOS - delivered | Birth or delivery |
| L222.11 | Assisted breech delivery | Birth or delivery |
| L222.12 | Breech delivery | Birth or delivery |
| L222.13 | Spontaneous breech delivery | Birth or delivery |
| L228100 | Multiple pregnancy with malpresentation - delivered | Birth or delivery |
| L22y100 | Other fetal malposition and malpresentation - delivered | Birth or delivery |
| L22z100 | Fetal malposition and malpresentation NOS - delivered | Birth or delivery |
| L296.00 | Vaginal delivery following previous caesarean section | Birth or delivery |
| L395.00 | Forceps delivery | Birth or delivery |
| L395.11 | Keilland's forceps delivery | Birth or delivery |
| L395.12 | Neville - Barnes forceps delivery | Birth or delivery |
| L395.13 | Simpson's forceps delivery | Birth or delivery |
| L395000 | Forceps delivery unspecified | Birth or delivery |
| L395100 | Forceps delivery - delivered | Birth or delivery |
| L395200 | Low forceps delivery | Birth or delivery |
| L395300 | Mid-cavity forceps delivery | Birth or delivery |
| L395400 | Delivery by combination of forceps and vacuum extractor | Birth or delivery |
| L395500 | Mid-cavity forceps with rotation | Birth or delivery |
| L395z00 | Forceps delivery NOS | Birth or delivery |
| L396.00 | Vacuum extractor delivery | Birth or delivery |
| L396.11 | Ventouse delivery | Birth or delivery |
| L396000 | Vacuum extractor delivery unspecified | Birth or delivery |
| L396100 | Vacuum extractor delivery - delivered | Birth or delivery |
| L396z00 | Vacuum extractor delivery NOS | Birth or delivery |
| L397.00 | Breech extraction | Birth or delivery |
| L397000 | Breech extraction unspecified | Birth or delivery |
| L397100 | Breech extraction - delivered | Birth or delivery |
| L397z00 | Breech extraction NOS | Birth or delivery |
| L398.00 | Caesarean delivery | Birth or delivery |
| L398000 | Caesarean delivery unspecified | Birth or delivery |
| L398100 | Caesarean delivery - delivered | Birth or delivery |
| L398200 | Caesarean section - pregnancy at term | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| L398300 | Delivery by elective caesarean section | Birth or delivery |
| L398400 | Delivery by emergency caesarean section | Birth or delivery |
| L398500 | Delivery by caesarean hysterectomy | Birth or delivery |
| L398600 | Caesarean delivery following previous Caesarean delivery | Birth or delivery |
| L398z00 | Caesarean delivery NOS | Birth or delivery |
| Ly0..00 | Spontaneous vertex delivery | Birth or delivery |
| Ly1..00 | Spontaneous breech delivery | Birth or delivery |
| Lyu5.00 | [X]Delivery | Birth or delivery |
| Lyu5000 | [X]Other single spontaneous delivery | Birth or delivery |
| Lyu5100 | [X]Other and unspecified forceps delivery | Birth or delivery |
| Lyu5200 | [X]Other single delivery by caesarean section | Birth or delivery |
| Lyu5300 | [X]Other assisted breech delivery | Birth or delivery |
| Lyu5400 | [X]Other manipulation-assisted delivery | Birth or delivery |
| Lyu5500 | [X]Other specified assisted single delivery | Birth or delivery |
| Lyu5600 | [X]Other multiple delivery | Birth or delivery |
| Lyu5700 | [X]Assisted single delivery, unspecified | Birth or delivery |
| Lyu5800 | [X]Multiple delivery, unspecified | Birth or delivery |
| Q432.00 | Preterm delivery associated jaundice | Birth or delivery |
| Z1H4.00 | Pain relief in labour | Birth or delivery |
| Z213.00 | Care of mother in labour | Birth or delivery |
| Z23B400 | Contraction of uterus during labour | Birth or delivery |
| Z23G.00 | Uterine observation in labour | Birth or delivery |
| Z24..00 | Labour observations | Birth or delivery |
| Z241.00 | Labour established | Birth or delivery |
| Z241100 | Onset of labour induced | Birth or delivery |
| Z243.00 | Observation of first stage of labour | Birth or delivery |
| Z243100 | First stage of labour established | Birth or delivery |
| Z243300 | Progress of labour - first stage | Birth or delivery |
| Z243400 | Rapid first stage of labour | Birth or delivery |
| Z243411 | Rapid progress in first stage of labour | Birth or delivery |
| Z243500 | Normal length of first stage of labour | Birth or delivery |
| Z243600 | Slow progress in first stage of labour | Birth or delivery |
| Z243700 | Normal first stage of labour | Birth or delivery |
| Z243800 | First stage of labour problem | Birth or delivery |
| Z244.00 | Observation of pattern of labour | Birth or delivery |
| Z244100 | Observation of duration of labour | Birth or delivery |
| Z244200 | Long duration of labour | Birth or delivery |
| Z244300 | Short duration of labour | Birth or delivery |
| Z244400 | Late onset of labour | Birth or delivery |
| Z244411 | Postmature labour | Birth or delivery |
| Z244500 | Relation of onset of labour to due date | Birth or delivery |
| Z245.00 | Observation of blood loss in labour | Birth or delivery |
| Z246.00 | Observation of measures of labour | Birth or delivery |
| Z246100 | Duration of labour | Birth or delivery |
| Z246111 | Length of labour | Birth or delivery |
| Z246200 | Onset of labour first stage | Birth or delivery |
| Z246211 | Start of labour | Birth or delivery |
| Z246311 | Onset of labour pains | Birth or delivery |
| Z246700 | Onset of second stage of labour | Birth or delivery |
| Z246900 | Duration of second stage of labour | Birth or delivery |
| Z246A00 | Total duration of labour | Birth or delivery |
| Z247.00 | Device-associated observation of labour | Birth or delivery |
| Z247100 | Expulsion of IUCD during third stage of labour | Birth or delivery |
| Z248.00 | Normal labour | Birth or delivery |
| Z249.00 | Labour problem | Birth or delivery |
| Z25..00 | Delivery observations | Birth or delivery |
| Z251.00 | Mother delivered | Birth or delivery |
| Z253.00 | Observation of speed of delivery | Birth or delivery |
| Z253.11 | Speed of delivery | Birth or delivery |
| Z253.12 | Rate of delivery | Birth or delivery |
| Z253100 | Slow rate of delivery | Birth or delivery |
| Z253200 | Rapid rate of delivery | Birth or delivery |
| Z253211 | Precipitate delivery | Birth or delivery |
| Z253300 | Normal rate of delivery | Birth or delivery |
| Z254.00 | Observation of pattern of delivery | Birth or delivery |
| Z254100 | Deliveries by forceps - delivered | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| Z254200 | Delivered by low forceps delivery | Birth or delivery |
| Z254300 | Delivered by mid-cavity forceps delivery | Birth or delivery |
| Z254400 | Deliveries by breech extraction | Birth or delivery |
| Z254500 | Delivered by caesarean section - pregnancy at term | Birth or delivery |
| Z254600 | Deliv caes following prev caes | Birth or delivery |
| Z254700 | Deliveries by vacuum extractor | Birth or delivery |
| Z254800 | Deliveries by spontaneous breech delivery | Birth or delivery |
| Z254900 | Vaginal delivery | Birth or delivery |
| Z254A00 | Abnormal delivery | Birth or delivery |
| Z254B00 | Brow delivery | Birth or delivery |
| Z254C00 | Face delivery | Birth or delivery |
| Z254D00 | Face to pubes birth | Birth or delivery |
| Z254E00 | Multiple birth | Birth or delivery |
| Z254E11 | Multiple birth delivery | Birth or delivery |
| Z255.00 | Observation of second stage of labour | Birth or delivery |
| Z255100 | Second stage of labour established | Birth or delivery |
| Z255200 | Second stage of labour not established | Birth or delivery |
| Z255300 | Progess of second stage of labour | Birth or delivery |
| Z255311 | Progess of delivery | Birth or delivery |
| Z255400 | Rapid second stage of labour | Birth or delivery |
| Z255600 | Normal length of second stage of labour | Birth or delivery |
| Z255700 | Failure to progress in second stage of labour | Birth or delivery |
| Z255711 | No progress with delivery | Birth or delivery |
| Z255712 | No progress in second stage of labour | Birth or delivery |
| Z255800 | Second stage of labour problem | Birth or delivery |
| Z255900 | Normal second stage of labour | Birth or delivery |
| Z255A00 | Observation of delivery push in labour | Birth or delivery |
| Z255B11 | Wants to push in labour | Birth or delivery |
| Z255C00 | No desire to push in labour | Birth or delivery |
| Z255D00 | Ability to push in labour | Birth or delivery |
| Z255D11 | Observation of ability to push in labour | Birth or delivery |
| Z255E00 | Pushing effectively in labour | Birth or delivery |
| Z255E11 | Pushing well in labour | Birth or delivery |
| Z255F00 | Not pushing well in labour | Birth or delivery |
| Z255G00 | Urge to push in labour | Birth or delivery |
| Z255H00 | Reluctant to push in labour | Birth or delivery |
| Z255I00 | Pushing voluntarily in labour | Birth or delivery |
| Z255J00 | Pushing involuntarily in labour | Birth or delivery |
| Z256.00 | Observation of third stage of labour | Birth or delivery |
| Z256100 | Normal length of third stage of labour | Birth or delivery |
| Z256200 | Prolonged third stage of labour | Birth or delivery |
| Z256300 | Speed of delivery of placenta | Birth or delivery |
| Z256311 | Rate of delivery of placenta | Birth or delivery |
| Z257.00 | Delivery normal | Birth or delivery |
| Z257.11 | Normal delivery | Birth or delivery |
| Z257.12 | Spontaneous vaginal delivery | Birth or delivery |
| Z257.13 | SVD - Spontaneous vaginal delivery | Birth or delivery |
| Z257.14 | FTND - Full term normal delivery | Birth or delivery |
| Z257.15 | ND - Normal delivery | Birth or delivery |
| Z257100 | Spontaneous vertex delivery | Birth or delivery |
| Z258.00 | Delivery problem | Birth or delivery |
| Z262600 | Complete placenta at delivery | Birth or delivery |
| Z262700 | Incomplete placenta at delivery | Birth or delivery |
| Z262711 | Incomplete delivery of placenta | Birth or delivery |
| Z263300 | Condition of membranes at delivery | Birth or delivery |
| Z265900 | Umbilical cord not around baby's neck at delivery | Birth or delivery |
| ZV24000 | [V]Examination immediately after delivery | Birth or delivery |
| ZV27.00 | [V]Outcome of delivery | Birth or delivery |
| ZV27.11 | [V]Live birth | Birth or delivery |
| ZV27.13 | [V]Birth - type | Birth or delivery |
| ZV27000 | [V]Single live birth | Birth or delivery |
| ZV27200 | [V]Twins, both live born | Birth or delivery |
| ZV27300 | [V]Twins, one live born and one stillborn | Birth or delivery |
| ZV27500 | [V]Other multiple birth, all live born | Birth or delivery |
| ZV27600 | [V]Other multiple birth, some live born | Birth or delivery |
| ZV27y00 | [V]Other specified outcome of delivery | Birth or delivery |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| ZV27z00 | [V]Unspecified delivery outcome | Birth or delivery |
| ZV3..00 | [V]Healthy liveborn infants according to type of birth | Birth or delivery |
| ZV31.00 | [V]Twin, mate live born | Birth or delivery |
| ZV31000 | [V]Twin, born in hospital, mate live born | Birth or delivery |
| ZV31100 | [V]Twin, born before admission to hospital, mate live born | Birth or delivery |
| ZV31200 | [V]Twin, not hospitalised, mate live born | Birth or delivery |
| ZV31z00 | [V]Twin, mate liveborn, NOS | Birth or delivery |
| ZV34.00 | [V]Other multiple birth, mates live born | Birth or delivery |
| ZV34000 | [V]Other multiple birth, born in hospital, mates live born | Birth or delivery |
| ZV34100 | [V]Other multiple birth, born before hospital, mates live | Birth or delivery |
| ZV34200 | [V]Other multiple birth, not hospitalised, mates live born | Birth or delivery |
| ZV34z00 | [V]Other multiple birth, mates live born, NOS | Birth or delivery |
| ZV36.00 | [V]Other multiple birth, mates live and stillborn | Birth or delivery |
| ZV36000 | [V]Other multiple birth, born in hospital, mates live+still | Birth or delivery |
| ZV36z00 | [V]Other multiple birth, mates live and stillborn NOS | Birth or delivery |
| ZV3y.00 | [V]Other multiple birth, unspecified | Birth or delivery |
| ZV3y000 | [V]Other multiple birth, unspecified, born in hospital | Birth or delivery |
| ZV3y100 | [V]Other multiple birth, unspecified, born before hospital | Birth or delivery |
| ZV3y200 | [V]Other multiple birth, unspecified, not hospitalised | Birth or delivery |
| ZV3yz00 | [V]Other multiple birth, unspecified, NOS | Birth or delivery |
| ZV3z.00 | [V]Unspecified birth | Birth or delivery |
| ZV3z000 | [V]Unspecified birth, born in hospital | Birth or delivery |
| ZV3z100 | [V]Unspecified birth, born before admission to hospital | Birth or delivery |
| ZV3z200 | [V]Unspecified birth, not hospitalised | Birth or delivery |
| ZV3zz00 | [V]Unspecified birth, NOS | Birth or delivery |
| ZVu2A00 | [X]Other multiple births, all liveborn | Birth or delivery |
| ZVu2B00 | [X]Other multiple births, some liveborn | Birth or delivery |
| ZVu2D00 | [X]Other multiple liveborn infants, born in hospital | Birth or delivery |
| ZVu2E00 | [X]Other multiple liveborn infants, born outside hospital | Birth or delivery |
| ZVu2F00 | [X]Oth multip liveborn infants, unspec as to place of birth | Birth or delivery |
| 632..00 | Length of labour | Length of labour |
| 6321.00 | 1st stage of labour length | Length of labour |
| 6322.00 | 2nd stage of labour length | Length of labour |
| 6323.00 | 3rd stage of labour length | Length of labour |
| 632Z.00 | Length of labour NOS | Length of labour |
| 14Y0.00 | Born by caesarean section | Mode of birth |
| 14Y1.00 | Born by forceps delivery | Mode of birth |
| 14Y2.00 | Born by elective caesarean section | Mode of birth |
| 14Y3.00 | Born by normal vaginal delivery | Mode of birth |
| 14Y4.00 | Born by breech delivery | Mode of birth |
| 14Y5.00 | Born by ventouse delivery | Mode of birth |
| 14Y6.00 | Born by emergency caesarean section | Mode of birth |
| 634..00 | Sex of baby | Sex of baby |
| 634..11 | Delivery - sex of baby | Sex of baby |
| 634..12 | Female baby | Sex of baby |
| 634..13 | Male baby | Sex of baby |
| 6341.00 | Baby male | Sex of baby |
| 6342.00 | Baby female | Sex of baby |
| 6343.00 | 2 male babies | Sex of baby |
| 6344.00 | 2 female babies | Sex of baby |
| 6345.00 | 1 male + 1 female baby | Sex of baby |
| 6346.00 | 3 male babies | Sex of baby |
| 6347.00 | 2 male + 1 female babies | Sex of baby |
| 6348.00 | 1 male + 2 female babies | Sex of baby |
| 6349.00 | 3 female babies | Sex of baby |
| 634Z.00 | Sex of baby NOS | Sex of baby |
| 6351.00 | Baby premature 36-38 weeks | Gestational age |
| 6352.00 | Baby v. premature 32-36 weeks | Gestational age |
| 6353.00 | Baby extremely prem.28-32 week | Gestational age |
| 6354.00 | Baby full term maturity | Gestational age |
| 6355.00 | Baby post-mature | Gestational age |
| 6356.00 | Baby premature 26-28 weeks | Gestational age |
| 6357.00 | Baby premature 24-26 weeks | Gestational age |
| 6358.00 | Baby premature 39 weeks | Gestational age |
| 6359.00 | Baby premature 38 weeks | Gestational age |
| 635A.00 | Baby premature 37 weeks | Gestational age |

**Table G.3** Continued.

| Read code | Code description | Category |
|---|---|---|
| 635B.00 | Baby premature 36 weeks | Gestational age |
| 635C.00 | Preterm infant status | Gestational age |
| 635C.11 | Preterm | Gestational age |
| 635Z.00 | Baby maturity NOS | Gestational age |
| 62R..12 | New birth visit | Postnatal visit |
| 62R1.00 | P/N - first day visit | Postnatal visit |
| 62R2.00 | P/N - second day visit | Postnatal visit |
| 62R3.00 | P/N - third day visit | Postnatal visit |
| 62R4.00 | P/N - fourth day visit | Postnatal visit |
| 62R5.00 | P/N - fifth day visit | Postnatal visit |
| 62R6.00 | P/N - sixth day visit | Postnatal visit |
| 62R7.00 | P/N - seventh day visit | Postnatal visit |
| 62R8.00 | P/N - eighth day visit | Postnatal visit |
| 62R9.00 | P/N - ninth day visit | Postnatal visit |
| 62RA.00 | P/N - tenth day visit | Postnatal visit |
| 9NFS.00 | Health visitor new birth visit | Postnatal visit |
| 44qW100 | Completion of newborn blood spot screening card | Postnatal care |
| 62RB.00 | P/N care started at birth | Postnatal care |
| 62RC.00 | P/N care <48hrs after birth | Postnatal care |
| 62RD.00 | P/N care >48hrs after birth | Postnatal care |
| 62S..00 | Maternal P/N 6 week exam. | Postnatal examination |
| 62S..11 | Postnatal exam. - maternal | Postnatal examination |
| 62S5.00 | Maternal P/N exam. done | Postnatal examination |
| 62SZ.00 | Maternal P/N 6 week exam. NOS | Postnatal examination |
| 68Y..00 | Newborn hearing screening | Hearing screen |
| 9Oq9G00 | Newborn hearing screening not done | Hearing screen |
| 9114.11 | FP58 - newborn registration | Newborn registration |
| 9114.12 | GP58 - newborn registration | Newborn registration |
| 9G7..00 | Notification of birth | Newborn registration |

**Table G.4** Read codes related to liver disease.

| Read code | Code description |
|---|---|
| 14S8.00 | H/O: liver recipient |
| 67P4200 | Discussion about liver transplantation |
| 7800.00 | Transplantation of liver |
| 7800000 | Orthotopic transplantation of liver |
| 7800100 | Heterotopic transplantation of liver |
| 7800111 | Auxillary liver transplant |
| 7800112 | Piggy back liver transplant |
| 7800200 | Replacement of previous liver transplant |
| 7800300 | Transplantation of liver cells |
| 7800400 | Orthotopic transplantation of whole liver |
| 7800500 | Orthotopic transplantation of liver NEC |
| 7800y00 | Other specified transplantation of liver |
| 7800z00 | Transplantation of liver NOS |
| 7805211 | Exploration of liver transplant |
| 7822011 | Kasai hepatojejunostomy + insertion tubal prosthesis |
| 7824400 | Roux-en-y procedure for biliary atresia |
| 7824411 | Sawaguchi roux-en-y procedure for biliary atresia |
| 7L1f.00 | Compensation for liver failure |
| 7L1fy00 | Other specified compensation for liver failure |
| 7L1fz00 | Compensation for liver failure NOS |
| 8LH..00 | Liver transplant planned |
| 9kR..00 | Chronic hepatitis annual review - enhanced services admin |
| 9kR..11 | Chronic hepatitis annual review |
| A707.00 | Chronic viral hepatitis |
| A707000 | Chronic viral hepatitis B with delta-agent |
| A707100 | Chronic viral hepatitis B without delta-agent |
| A707200 | Chronic viral hepatitis C |
| A707300 | Chronic viral hepatitis B |
| A707X00 | Chronic viral hepatitis, unspecified |
| AC11.11 | Chinese liver fluke disease |
| AyuB100 | [X]Other chronic viral hepatitis |
| AyuB200 | [X]Chronic viral hepatitis, unspecified |
| C310400 | Glycogenosis with hepatic cirrhosis |
| C350000 | Haemochromatosis |
| C350012 | Pigmentary cirrhosis of liver |
| C370700 | Liver disease due to cystic fibrosis |
| C370800 | Cystic fibrosis related cirrhosis |
| C376100 | Alpha-1-antitrypsin hepatitis |
| C376200 | Alpha-1-antitrypsin deficiency |
| D307000 | Deficiency of coagulation factor due to liver disease |
| G820.00 | Budd - Chiari syndrome (hepatic vein thrombosis) |
| G852200 | Oesophageal varices in cirrhosis of the liver |
| G852300 | Oesophageal varices in alcoholic cirrhosis of the liver |
| J6...00 | Liver, biliary, pancreas + gastrointestinal diseases NEC |
| J60..00 | Acute and subacute liver necrosis |
| J600.00 | Acute necrosis of liver |
| J600000 | Acute hepatic failure |
| J600011 | Acute liver failure |
| J600100 | Acute hepatitis - noninfective |
| J600200 | Acute yellow atrophy |
| J600z00 | Acute necrosis of liver NOS |
| J601.00 | Subacute necrosis of liver |
| J601000 | Subacute hepatic failure |
| J601100 | Subacute hepatitis - noninfective |
| J601200 | Subacute yellow atrophy |
| J601z00 | Subacute necrosis of liver NOS |
| J60z.00 | Acute and subacute liver necrosis NOS |
| J61..00 | Cirrhosis and chronic liver disease |
| J610.00 | Alcoholic fatty liver |
| J611.00 | Acute alcoholic hepatitis |
| J612.00 | Alcoholic cirrhosis of liver |
| J612.11 | Florid cirrhosis |
| J612.12 | Laennec's cirrhosis |

**Table G.4** Continued.

| Read code | Code description |
|---|---|
| J612000 | Alcoholic fibrosis and sclerosis of liver |
| J613.00 | Alcoholic liver damage unspecified |
| J613000 | Alcoholic hepatic failure |
| J614.00 | Chronic hepatitis |
| J614000 | Chronic persistent hepatitis |
| J614100 | Chronic active hepatitis |
| J614111 | Autoimmune chronic active hepatitis |
| J614200 | Chronic aggressive hepatitis |
| J614300 | Recurrent hepatitis |
| J614400 | Chronic lobular hepatitis |
| J614y00 | Chronic hepatitis unspecified |
| J614z00 | Chronic hepatitis NOS |
| J615.00 | Cirrhosis - non alcoholic |
| J615.11 | Portal cirrhosis |
| J615000 | Unilobular portal cirrhosis |
| J615100 | Multilobular portal cirrhosis |
| J615111 | Postnecrotic cirrhosis of liver |
| J615200 | Mixed portal cirrhosis |
| J615300 | Diffuse nodular cirrhosis |
| J615400 | Fatty portal cirrhosis |
| J615500 | Hypertrophic portal cirrhosis |
| J615600 | Capsular portal cirrhosis |
| J615700 | Cardiac portal cirrhosis |
| J615711 | Congestive cirrhosis |
| J615800 | Juvenile portal cirrhosis |
| J615811 | Childhood function cirrhosis |
| J615812 | Indian childhood cirrhosis |
| J615900 | Pigmentary portal cirrhosis |
| J615A00 | Pipe-stem portal cirrhosis |
| J615B00 | Toxic portal cirrhosis |
| J615C00 | Xanthomatous portal cirrhosis |
| J615D00 | Bacterial portal cirrhosis |
| J615E00 | Cardituberculous cirrhosis |
| J615F00 | Syphilitic portal cirrhosis |
| J615G00 | Zooparasitic portal cirrhosis |
| J615H00 | Infectious cirrhosis NOS |
| J615y00 | Portal cirrhosis unspecified |
| J615z00 | Non-alcoholic cirrhosis NOS |
| J615z11 | Macronodular cirrhosis of liver |
| J615z12 | Cryptogenic cirrhosis of liver |
| J615z13 | Cirrhosis of liver NOS |
| J615z14 | Laennec's cirrhosis, non-alcoholic |
| J615z15 | Hepatic fibrosis |
| J616.00 | Biliary cirrhosis |
| J616000 | Primary biliary cirrhosis |
| J616100 | Secondary biliary cirrhosis |
| J616200 | Biliary cirrhosis of children |
| J616z00 | Biliary cirrhosis NOS |
| J617.00 | Alcoholic hepatitis |
| J617000 | Chronic alcoholic hepatitis |
| J61y.00 | Other non-alcoholic chronic liver disease |
| J61y000 | Chronic yellow liver atrophy |
| J61y100 | Non-alcoholic fatty liver |
| J61y200 | Hepatosplenomegaly |
| J61y300 | Portal fibrosis without cirrhosis |
| J61y400 | Hepatic fibrosis |
| J61y500 | Hepatic sclerosis |
| J61y600 | Hepatic fibrosis with hepatic sclerosis |
| J61y700 | Steatosis of liver |
| J61y800 | Nonalcoholic steatohepatitis |
| J61y900 | Fatty change of liver |
| J61y911 | Fatty liver |
| J61yz00 | Other non-alcoholic chronic liver disease NOS |
| J61z.00 | Chronic liver disease NOS |

**Table G.4** Continued.

| Read code | Code description |
|---|---|
| J62..00 | Liver abscess and sequelae of chronic liver disease |
| J620.00 | Liver abscess - excluding amoebic liver abscess |
| J620000 | Liver abscess due to portal pyaemia |
| J620100 | Liver abscess due to cholangitis |
| J620200 | Liver abscess via hepatic artery |
| J620300 | Liver abscess via umbilicus |
| J620400 | Liver abscess due to direct extension |
| J620z00 | Liver abscess NOS |
| J621.00 | Portal pyaemia |
| J621.11 | Phlebitis of portal vein |
| J622.00 | Hepatic coma |
| J622.11 | Encephalopathy - hepatic |
| J623.00 | Portal hypertension |
| J624.00 | Hepatorenal syndrome |
| J625.00 | [X] Hepatic failure |
| J625.11 | [X] Liver failure |
| J62y.00 | Other sequelae of chronic liver disease |
| J62y.11 | Hepatic failure NOS |
| J62y.12 | Liver failure NOS |
| J62y.13 | Hepatic failure |
| J62z.00 | Liver abscess and chronic liver disease causing sequelae NOS |
| J635.00 | Toxic liver disease |
| J635000 | Toxic liver disease with cholestasis |
| J635100 | Toxic liver disease with hepatic necrosis |
| J635200 | Toxic liver disease with acute hepatitis |
| J635300 | Toxic liver disease with chronic persistent hepatitis |
| J635400 | Toxic liver disease with chronic lobular hepatitis |
| J635500 | Toxic liver disease with chronic active hepatitis |
| J635600 | Toxic liver disease with fibrosis and cirrhosis of liver |
| J635700 | Acute hepatic failure due to drugs |
| J635X00 | Toxic liver disease, unspecified |
| J637.00 | Hepatic veno-occlusive disease |
| J63B.00 | Autoimmune hepatitis |
| J66..00 | Other biliary tract disorders |
| J660.00 | Postcholecystectomy syndrome |
| J661.00 | Cholangitis |
| J661000 | Acute cholangitis |
| J661100 | Chronic cholangitis |
| J661200 | Recurrent cholangitis |
| J661300 | Suppurative cholangitis |
| J661400 | Ascending cholangitis |
| J661500 | Cholangitis lenta |
| J661600 | Obliterative cholangitis |
| J661700 | Primary sclerosing cholangitis |
| J661800 | Secondary sclerosing cholangitis |
| J661900 | Sclerosing cholangitis unspecified |
| J661y00 | Other cholangitis |
| J661z00 | Cholangitis NOS |
| J662.00 | Obstruction of bile duct |
| J662000 | Occlusion of bile duct |
| J662100 | Stricture of bile duct |
| J662z00 | Obstruction of bile duct NOS |
| J663.00 | Perforation of bile duct |
| J664.00 | Fistula of bile duct |
| J664000 | Choledochoduodenal fistula |
| J664z00 | Fistula of bile duct NOS |
| J665.00 | Spasm of sphincter of Oddi |
| J666.00 | Biliary sepsis |
| J66y.00 | Other bile duct disorders |
| J66y000 | Adhesions of bile duct |
| J66y100 | Atrophy of bile duct |
| J66y200 | Cyst of bile duct |
| J66y300 | Hypertrophy of bile duct |
| J66y400 | Stasis of bile duct |

**Table G.4** Continued.

| Read code | Code description |
|---|---|
| J66y500 | Ulcer of bile duct |
| J66y600 | Obstructive jaundice NOS |
| J66y700 | Post cholecystectomy bile leakage |
| J66yz00 | Other bile duct disorder NOS |
| J66z.00 | Bile duct disorder NOS |
| J6y..00 | Liver, biliary, pancreas + gastrointestinal diseases OS |
| J6z..00 | Liver, biliary, pancreas + gastrointestinal diseases NOS |
| Jyu7.00 | [X]Diseases of the liver |
| Jyu7000 | [X]Toxic liver disease with other disorders of liver |
| Jyu7100 | [X]Other and unspecified cirrhosis of liver |
| Jyu7200 | [X]Other specified inflammatory liver diseases |
| Jyu7300 | [X]Other specified diseases of liver |
| Jyu7400 | [X]Liver disorders in infectious and parasitic diseases CE |
| Jyu7500 | [X]Liver disorders in other diseases classified elsewhere |
| Jyu7600 | [X]Toxic liver disease, unspecified |
| Jyu7700 | [X]Granulomatous hepatitis, not elsewhere classified |
| PB6..00 | Liver and biliary system anomalies |
| PB6..11 | Bile duct anomalies |
| PB6..12 | Biliary anomalies |
| PB6..13 | Gallbladder anomalies |
| PB6..14 | Liver anomalies |
| PB60.00 | Liver and biliary system anomalies, unspecified |
| PB60000 | Liver anomaly, unspecified |
| PB60100 | Gallbladder anomaly, unspecified |
| PB60200 | Bile duct anomaly, unspecified |
| PB60z00 | Unspecified liver and biliary system anomaly NOS |
| PB61.00 | Biliary atresia |
| PB61.11 | Bile duct atresia |
| PB61000 | Congenital absence of bile duct |
| PB61011 | Agenesis of bile duct |
| PB61100 | Congenital hypoplasia of bile duct |
| PB61200 | Congenital obstruction of bile duct |
| PB61300 | Congenital stricture of bile duct |
| PB61311 | Congenital stricture of common bile duct |
| PB61400 | Atresia of bile duct |
| PB61411 | Intrahepatic atresia of bile duct |
| PB61412 | Extrahepatic atresia of bile duct |
| PB61500 | Congenital absence of hepatic ducts |
| PB61511 | Agenesis of hepatic ducts |
| PB61600 | Atresia of hepatic ducts |
| PB61z00 | Biliary atresia NOS |
| PB62.00 | Congenital cystic liver disease |
| PB62.11 | Congenital hepatic cyst |
| PB62000 | Congenital polycystic liver disease |
| PB62100 | Fibrocystic liver disease |
| PB62z00 | Congenital cystic liver disease NOS |
| PB63.00 | Congenital absence of liver and gallbladder |
| PB63000 | Congenital absence of gallbladder |
| PB63011 | Agenesis of gallbladder |
| PB63100 | Congenital absence of liver lobe |
| PB63111 | Congenital agenesis of liver lobe |
| PB63200 | Congenital small left lobe of liver |
| PB63300 | Riedel's lobe liver |
| PB63400 | Congenital absence of liver,total |
| PB63411 | Congenital agenesis liver,total |
| PB63500 | Alagille syndrome |
| PB63z00 | Absence of liver or gallbladder NOS |
| PB64.00 | Liver and biliary duplication |
| PB64000 | Duplication of biliary duct |
| PB64100 | Duplication of cystic duct |
| PB64200 | Duplication of gallbladder |
| PB64300 | Duplication of liver |
| PB64311 | Accessory liver |
| PB64400 | Accessory hepatic ducts |

**Table G.4** Continued.

| Read code | Code description |
|---|---|
| PB64z00 | Liver or biliary duplication NOS |
| PB6y.00 | Other liver and biliary anomalies |
| PB6y000 | Congenital choledochal cyst |
| PB6y100 | Congenital hepatomegaly |
| PB6y200 | Congenital floating gallbladder |
| PB6y300 | Congenital floating liver |
| PB6y400 | Intrahepatic gallbladder |
| PB6y500 | Hypoplasia of gallbladder |
| PB6y600 | Atrophy of left lobe of liver |
| PB6y700 | Congenital dilation of bile duct |
| PB6y800 | Congenital diverticulum of bile duct |
| PB6y900 | Liver hyperplasia |
| PB6yw00 | Other congenital anomaly of liver |
| PB6yw11 | Liver hamartoma |
| PB6yw12 | Abnormal liver lobulation |
| PB6yw13 | Trilobular liver |
| PB6yx00 | Other congenital anomaly of gallbladder |
| PB6yy00 | Other congenital anomaly of hepatic or bile ducts |
| PB6yy11 | Congenital kink of cystic duct |
| PB6yz00 | Other liver or biliary system anomalies NOS |
| PB6z.00 | Liver or biliary system anomalies NOS |
| SP08600 | Liver transplant failure and rejection |
| SP14200 | Hepatic failure as a complication of care |
| SP14211 | Liver failure as a complication of care |
| TB00200 | Liver transplant with complication, without blame |
| ZC2CH11 | Dietary advice for liver disease |
| ZV42700 | [V]Liver transplanted |
| ZV7C000 | [V]Assessment for liver transplant |

**Table G.5** Read codes related to chronic kidney disease.

| Read code | Code description |
|---|---|
| 14S2.00 | H/O: kidney recipient |
| 14V2.00 | H/O: renal dialysis |
| 14V2.11 | H/O: kidney dialysis |
| 1Z1..00 | Chronic renal impairment |
| 1Z10.00 | Chronic kidney disease stage 1 |
| 1Z11.00 | Chronic kidney disease stage 2 |
| 1Z12.00 | Chronic kidney disease stage 3 |
| 1Z13.00 | Chronic kidney disease stage 4 |
| 1Z14.00 | Chronic kidney disease stage 5 |
| 1Z15.00 | Chronic kidney disease stage 3A |
| 1Z16.00 | Chronic kidney disease stage 3B |
| 1Z17.00 | Chronic kidney disease stage 1 with proteinuria |
| 1Z17.11 | CKD stage 1 with proteinuria |
| 1Z18.00 | Chronic kidney disease stage 1 without proteinuria |
| 1Z18.11 | CKD stage 1 without proteinuria |
| 1Z19.00 | Chronic kidney disease stage 2 with proteinuria |
| 1Z19.11 | CKD stage 2 with proteinuria |
| 1Z1A.00 | Chronic kidney disease stage 2 without proteinuria |
| 1Z1A.11 | CKD stage 2 without proteinuria |
| 1Z1B.00 | Chronic kidney disease stage 3 with proteinuria |
| 1Z1B.11 | CKD stage 3 with proteinuria |
| 1Z1C.00 | Chronic kidney disease stage 3 without proteinuria |
| 1Z1C.11 | CKD stage 3 without proteinuria |
| 1Z1D.00 | Chronic kidney disease stage 3A with proteinuria |
| 1Z1D.11 | CKD stage 3A with proteinuria |
| 1Z1E.00 | Chronic kidney disease stage 3A without proteinuria |
| 1Z1E.11 | CKD stage 3A without proteinuria |
| 1Z1F.00 | Chronic kidney disease stage 3B with proteinuria |
| 1Z1F.11 | CKD stage 3B with proteinuria |
| 1Z1G.00 | Chronic kidney disease stage 3B without proteinuria |
| 1Z1G.11 | CKD stage 3B without proteinuria |
| 1Z1H.00 | Chronic kidney disease stage 4 with proteinuria |
| 1Z1H.11 | CKD stage 4 with proteinuria |
| 1Z1J.00 | Chronic kidney disease stage 4 without proteinuria |
| 1Z1J.11 | CKD stage 4 without proteinuria |
| 1Z1K.00 | Chronic kidney disease stage 5 with proteinuria |
| 1Z1K.11 | CKD stage 5 with proteinuria |
| 1Z1L.00 | Chronic kidney disease stage 5 without proteinuria |
| 1Z1L.11 | CKD stage 5 without proteinuria |
| 661M200 | Chronic kidney disease self-management plan agreed |
| 661N200 | Chronic kidney disease self-management plan review |
| 66i..00 | Chronic kidney disease monitoring |
| 67P4100 | Discussion about kidney transplantation |
| 6AA..00 | Chronic kidney disease annual review |
| 7A60600 | Creation of graft fistula for dialysis |
| 7A61900 | Ligation of arteriovenous dialysis fistula |
| 7A61A00 | Ligation of arteriovenous dialysis graft |
| 7B00.00 | Transplantation of kidney |
| 7B00000 | Autotransplant of kidney |
| 7B00100 | Transplantation of kidney from live donor |
| 7B00111 | Allotransplantation of kidney from live donor |
| 7B00200 | Transplantation of kidney from cadaver |
| 7B00211 | Allotransplantation of kidney from cadaver |
| 7B00212 | Cadaveric renal transplant |
| 7B00300 | Allotransplantation of kidney from cadaver, heart-beating |
| 7B00400 | Allotransplantation kidney from cadaver, heart non-beating |
| 7B00500 | Allotransplantation of kidney from cadaver NEC |
| 7B00600 | Xenograft renal transplant |
| 7B00y00 | Other specified transplantation of kidney |
| 7B00z00 | Transplantation of kidney NOS |
| 7B01511 | Excision of rejected transplanted kidney |
| 7B01900 | Excision of rejected transplanted kidney |
| 7B03300 | Rovsing's operation for polycystic kidney |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| 7B06300 | Exploration of renal transplant |
| 7B0F.00 | Interventions associated with transplantation of kidney |
| 7B0F100 | Pre-transplantation of kidney work-up, recipient |
| 7B0F300 | Post-transplantation of kidney examination, recipient |
| 7B0Fy00 | OS interventions associated with transplantation of kidney |
| 7B0Fz00 | Interventions associated with transplantation of kidney NOS |
| 7L1A.00 | Compensation for renal failure |
| 7L1A.11 | Dialysis for renal failure |
| 7L1A000 | Renal dialysis |
| 7L1A011 | Thomas intravascular shunt for dialysis |
| 7L1A100 | Peritoneal dialysis |
| 7L1A200 | Haemodialysis NEC |
| 7L1A400 | Automated peritoneal dialysis |
| 7L1A500 | Continuous ambulatory peritoneal dialysis |
| 7L1A600 | Peritoneal dialysis NEC |
| 7L1Ay00 | Other specified compensation for renal failure |
| 7L1Az00 | Compensation for renal failure NOS |
| 7L1B.00 | Placement ambulatory apparatus compensation renal failure |
| 7L1B.11 | Placement ambulatory dialysis apparatus - compens renal fail |
| 7L1B000 | Insertion of ambulatory peritoneal dialysis catheter |
| 7L1B100 | Removal of ambulatory peritoneal dialysis catheter |
| 7L1B200 | Flushing of peritoneal dialysis catheter |
| 7L1By00 | Placement ambulatory apparatus- compensate renal failure OS |
| 7L1Bz00 | Placement ambulatory apparatus- compensate renal failure NOS |
| 7L1C.00 | Placement other apparatus for compensation for renal failure |
| 7L1C000 | Insertion of temporary peritoneal dialysis catheter |
| 7L1Cy00 | Placement other apparatus- compensate for renal failure OS |
| 7L1Cz00 | Placement other apparatus- compensate for renal failure NOS |
| 8L50.00 | Renal transplant planned |
| 9Ni9.00 | Did not attend chronic kidney disease monitoring clinic |
| 9Ot..00 | Chronic kidney disease monitoring administration |
| 9Ot0.00 | Chronic kidney disease monitoring first letter |
| 9Ot1.00 | Chronic kidney disease monitoring second letter |
| 9Ot2.00 | Chronic kidney disease monitoring third letter |
| 9Ot3.00 | Chronic kidney disease monitoring verbal invite |
| 9Ot4.00 | Chronic kidney disease monitoring telephone invite |
| 9Ot5.00 | Predicted stage chronic kidney disease |
| 9hE..00 | Exception reporting: chronic kidney disease quality indicato |
| 9hE0.00 | Except chronic kidney disease qual indic: Patient unsuitable |
| 9hE1.00 | Exc chronic kidney disease quality indicators: Inform dissen |
| A160000 | Tuberculous nephropathy |
| A844100 | Plasmodium malariae malaria with nephropathy |
| C300D00 | Infantile nephropathic cystinosis |
| C300y12 | Hypophosphataemic rickets with nephrotic-glycosuric dwarfism |
| C353600 | Renal failure-associated hyperphosphataemia |
| C354C00 | Cortical nephrocalcinosis |
| C373412 | Amyloid nephropathy with deafness and urticaria |
| C373L00 | Amyloid nephropathy of Ostertag |
| D215.00 | Anaemia secondary to renal failure |
| D215000 | Anaemia secondary to chronic renal failure |
| G22..00 | Hypertensive renal disease |
| G22..11 | Nephrosclerosis |
| G220.00 | Malignant hypertensive renal disease |
| G221.00 | Benign hypertensive renal disease |
| G222.00 | Hypertensive renal disease with renal failure |
| G22z.00 | Hypertensive renal disease NOS |
| G22z.11 | Renal hypertension |
| G23..00 | Hypertensive heart and renal disease |
| G230.00 | Malignant hypertensive heart and renal disease |
| G231.00 | Benign hypertensive heart and renal disease |
| G232.00 | Hypertensive heart&renal dis wth (congestive) heart failure |
| G233.00 | Hypertensive heart and renal disease with renal failure |
| G234.00 | Hyperten heart&renal dis+both(congestv)heart and renal fail |
| G23z.00 | Hypertensive heart and renal disease NOS |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| G721100 | Congenital renal artery aneurysm |
| G72C.00 | Ruptured aneurysm of dialysis vascular access |
| G72D.00 | Aneurysm of dialysis arteriovenous fistula |
| G72D000 | Aneurysm of superficialised artery of dialysis AV fistula |
| G72D100 | Aneurysm of needle site of dialysis arteriovenous fistula |
| G72D200 | Aneurysm of anastomotic site of dialysis AV fistula |
| G72E.00 | Aneurysm of dialysis vascular access |
| G752111 | Antiglomerular basement membrane disease |
| G752112 | Anti GBM disease - Antiglomerular basement membrane disease |
| Gy1..00 | Stenosis of dialysis vascular access |
| Gy10.00 | Stenosis of dialysis arteriovenous graft |
| Gy11.00 | Stenosis of dialysis arteriovenous shunt |
| Gy11000 | Stenosis of arterial side of dialysis arteriovenous shunt |
| Gy11100 | Stenosis of venous side of dialysis arteriovenous shunt |
| Gy2..00 | Thrombosis of dialysis vascular access |
| Gy20.00 | Thrombosis of dialysis arteriovenous graft |
| Gy21.00 | Thrombosis of dialysis arteriovenous fistula |
| Gy22.00 | Thrombosis of dialysis arteriovenous shunt |
| Gy3..00 | Occlusion of dialysis vascular access |
| Gy30.00 | Occlusion of dialysis arteriovenous graft |
| Gy31.00 | Occlusion of dialysis arteriovenous fistula |
| Gy32.00 | Occlusion of dialysis arteriovenous shunt |
| Gy4..00 | Infection of dialysis vascular access |
| Gy40.00 | Infection of dialysis arteriovenous graft |
| Gy41.00 | Infection of dialysis arteriovenous fistula |
| Gy42.00 | Infection of dialysis arteriovenous shunt |
| Gy5..00 | Haemorrhage of dialysis vascular access |
| Gy50.00 | Haemorrhage of dialysis arteriovenous graft |
| Gy51.00 | Haemorrhage of dialysis arteriovenous fistula |
| Gy52.00 | Haemorrhage of dialysis arteriovenous shunt |
| Gy6..00 | Rupture of dialysis vascular access |
| Gy60.00 | Rupture of dialysis arteriovenous graft |
| Gy61.00 | Rupture of dialysis arteriovenous fistula |
| Gy62.00 | Rupture of dialysis arteriovenous shunt |
| K0...00 | Nephritis, nephrosis and nephrotic syndrome |
| K000100 | Crescentic glomerulonephritis |
| K000111 | CGN - Crescentic glomerulonephritis |
| K01..00 | Nephrotic syndrome |
| K010.00 | Nephrotic syndrome with proliferative glomerulonephritis |
| K011.00 | Nephrotic syndrome with membranous glomerulonephritis |
| K012.00 | Nephrotic syndrome+membranoproliferative glomerulonephritis |
| K013.00 | Nephrotic syndrome with minimal change glomerulonephritis |
| K013.11 | Lipoid nephrosis |
| K013.12 | Steroid sensitive nephrotic syndrome |
| K014.00 | Nephrotic syndrome, minor glomerular abnormality |
| K015.00 | Nephrotic syndrome, focal and segmental glomerular lesions |
| K016.00 | Nephrotic syndrome, diffuse membranous glomerulonephritis |
| K017.00 | Nephrotic syn difus mesangial prolifertiv glomerulonephritis |
| K018.00 | Nephrotic syn,difus endocapilary proliftv glomerulonephritis |
| K019.00 | Nephrotic syn,diffuse mesangiocapillary glomerulonephritis |
| K01A.00 | Nephrotic syndrome, dense deposit disease |
| K01B.00 | Nephrotic syndrome, diffuse crescentic glomerulonephritis |
| K01w.00 | Congenital nephrotic syndrome |
| K01w000 | Finnish nephrosis syndrome |
| K01w011 | Microcystic type congenital nephrotic syndrome |
| K01w012 | Congenital Finnish nephrosis |
| K01w100 | Drash syndrome |
| K01w111 | Nephrotic syndrome with pseudohermaphroditism |
| K01w112 | Wilms' tumour + nephrotic syndrome + pseudohermaphroditism |
| K01w200 | Congenital nephrotic syndrome with focal glomerulosclerosis |
| K01wz00 | Congenital nephrotic syndrome NOS |
| K01x.00 | Nephrotic syndrome in diseases EC |
| K01x000 | Nephrotic syndrome in amyloidosis |
| K01x100 | Nephrotic syndrome in diabetes mellitus |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| K01x111 | Kimmelstiel - Wilson disease |
| K01x200 | Nephrotic syndrome in malaria |
| K01x300 | Nephrotic syndrome in polyarteritis nodosa |
| K01x400 | Nephrotic syndrome in systemic lupus erythematosus |
| K01x411 | Lupus nephritis |
| K01xz00 | Nephrotic syndrome in diseases EC NOS |
| K01y.00 | Nephrotic syndrome with other pathological kidney lesions |
| K01z.00 | Nephrotic syndrome NOS |
| K02..00 | Chronic glomerulonephritis |
| K02..11 | Nephritis - chronic |
| K02..12 | Nephropathy - chronic |
| K020.00 | Chronic proliferative glomerulonephritis |
| K021.00 | Chronic membranous glomerulonephritis |
| K022.00 | Chronic membranoproliferative glomerulonephritis |
| K023.00 | Chronic rapidly progressive glomerulonephritis |
| K024.00 | Thin basement membrane disease |
| K02y.00 | Other chronic glomerulonephritis |
| K02y000 | Chronic glomerulonephritis + diseases EC |
| K02y100 | Chronic exudative glomerulonephritis |
| K02y200 | Chronic focal glomerulonephritis |
| K02y300 | Chronic diffuse glomerulonephritis |
| K02y400 | Chronic radiation nephritis |
| K02yz00 | Other chronic glomerulonephritis NOS |
| K02z.00 | Chronic glomerulonephritis NOS |
| K03..00 | Nephritis and nephropathy unspecified |
| K03..11 | Nephritis and nephropathy unspecified |
| K03..12 | Nephropathy, unspecified |
| K030.00 | Proliferative nephritis unspecified |
| K031.00 | Membranous nephritis unspecified |
| K032.00 | Membranoproliferative nephritis unspecified |
| K032000 | Focal membranoproliferative glomerulonephritis |
| K032200 | Focal glomerulon + focal recurr macroscop glomerulonephritis |
| K032300 | Anaphylactoid glomerulonephritis |
| K032400 | Familial glomerulonephritis in Alport's syndrome |
| K032500 | Other familial glomerulonephritis |
| K032600 | Berger's IgA or IgG nephropathy |
| K032y00 | Nephritis unsp+OS membranoprolif glomerulonephritis lesion |
| K032y11 | Hypocomplementaemic persistent glomerulonephritis NEC |
| K032y12 | Lobular glomerulonephritis NEC |
| K032y13 | Mesangioproliferative glomerulonephritis NEC |
| K032y14 | Mesangiocapillary glomerulonephritis NEC |
| K032y15 | Mixed membranous and proliferative glomerulonephritis NEC |
| K032z00 | Nephritis unsp+membranoprolif glomerulonephritis lesion NOS |
| K033.00 | Rapidly progressive nephritis unspecified |
| K034.00 | Renal cortical necrosis unspecified |
| K035.00 | Renal medullary necrosis unspecified |
| K036.00 | Cryoglobulinaemic glomerulonephritis |
| K03T.00 | Tubulo-interstit nephritis, not specif as acute or chron |
| K03U.00 | Unspecif nephr synd, diff concentric glomerulonephritis |
| K03V.00 | Unspecified nephritic syndrome, dense deposit disease |
| K03W.00 | Unsp nephrit synd, diff endocap prolif glomerulonephritis |
| K03X.00 | Unsp nephrit synd, diff mesang prolif glomerulonephritis |
| K03y.00 | Other nephritis and nephrosis unspecified |
| K03y000 | Other nephritis and nephrosis in diseases EC |
| K03y100 | Other exudative nephritis |
| K03y200 | Other interstitial nephritis |
| K03yz00 | Other nephritis and nephrosis NOS |
| K03z.00 | Unspecified glomerulonephritis NOS |
| K05..00 | Chronic renal failure |
| K05..11 | Chronic uraemia |
| K05..12 | End stage renal failure |
| K05..13 | Chronic kidney disease |
| K050.00 | End stage renal failure |
| K051.00 | Chronic kidney disease stage 1 |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| K052.00 | Chronic kidney disease stage 2 |
| K053.00 | Chronic kidney disease stage 3 |
| K054.00 | Chronic kidney disease stage 4 |
| K055.00 | Chronic kidney disease stage 5 |
| K06..00 | Renal failure unspecified |
| K06..11 | Uraemia NOS |
| K06..12 | Kidney failure unspecified |
| K060.00 | Renal impairment |
| K060.11 | Impaired renal function |
| K07..00 | Renal sclerosis unspecified |
| K070.00 | Atrophy of kidney |
| K071.00 | Renal fibrosis |
| K072.00 | Glomerulosclerosis |
| K073.00 | Diffuse mesangial sclerosis with ocular abnormalities |
| K07z.00 | Renal sclerosis NOS |
| K08..00 | Impaired renal function disorder |
| K080.00 | Renal osteodystrophy |
| K080000 | Phosphate-losing tubular disorders |
| K080100 | Renal dwarfism |
| K080200 | Renal infantilism |
| K080300 | Renal rickets |
| K080z00 | Renal osteodystrophy NOS |
| K081100 | Congenital nephrogenic diabetes insipidus |
| K08y000 | Hypokalaemic nephropathy |
| K08y211 | Albright's renal tubular acidosis |
| K08y300 | Renal function impairment with growth failure |
| K08y400 | Renal tubular acidosis |
| K08y412 | Renal tubular acidaemia |
| K08y800 | Renal tubular acidosis with progressive nerve deafness |
| K08y900 | Classic distal renal tubular acidosis |
| K08yB00 | Hyperkalaemic renal tubular acidosis |
| K08yB11 | Type IV renal tubular acidosis |
| K08yC00 | Proximal renal tubular acidosis |
| K08yC11 | Type II renal tubular acidosis |
| K08yD00 | Distal renal tubular acidosis |
| K08yE00 | Mixed renal tubular acidosis |
| K08yE11 | Type III renal tubular acidosis |
| K08yH00 | Familial renal hypouricaemia |
| K08yz12 | Renotubular acidaemia |
| K08z.00 | Impaired renal function disorder NOS |
| K0A..00 | Glomerular disease |
| K0A1.00 | Rapidly progressive nephritic syndrome |
| K0A1000 | Rapid progres neph syndrome, minor glomerular abnormality |
| K0A1100 | Rapid progres nephritic syn focal+segmental glomerulr lesion |
| K0A1200 | Rapid progres neph syn diffuse membranous glomerulonephritis |
| K0A1300 | Rpd prog neph syn df mesangial prolifratv glomerulonephritis |
| K0A1400 | Rapid progres neph syn df endocapilary prolifv glomnephritis |
| K0A1500 | Rapid prog neph syn df mesangiocapillary glomerulonephritis |
| K0A1600 | Rapid progressive nephritic syndrome, dense deposit disease |
| K0A1700 | Rapid progres nephritic syn df crescentic glomerulonephritis |
| K0A2000 | Recurrent+persistnt haematuria minor glomerular abnormality |
| K0A2100 | Recur+persist haematuria, focal+segmental glomerular lesions |
| K0A2200 | Recur+persist haematuria difus membranous glomerulonephritis |
| K0A2300 | Recur+persist haemuria df mesangial prolif glomerulnephritis |
| K0A2400 | Recur+persist haemuria df endocaplry prolifrtv glomeruloneph |
| K0A2500 | Recur+persist hmuria df mesangiocapilary glomerulonephritis |
| K0A2700 | Recur+persist haematuria difus crescentic glomerulonephritis |
| K0A2800 | IgA nephropathy |
| K0A3.00 | Chronic nephritic syndrome |
| K0A3000 | Chronic nephritic syndrome, minor glomerular abnormality |
| K0A3100 | Chronic nephritic syndrm focal+segmental glomerular lesions |
| K0A3200 | Chron nephritic syndrom difuse membranous glomerulonephritis |
| K0A3300 | Chron neph syn difus mesangial prolifrtiv glomerulonephritis |
| K0A3400 | Chron neph syn difuse endocap prolifrativ glomerulonephritis |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| K0A3500 | Chronic neph syn difus mesangiocapillary glomerulonephritis |
| K0A3600 | Chronic nephritic syndrome, dense deposit disease |
| K0A3700 | Chronic nephritic syn diffuse crescentic glomerulonephritis |
| K0A5.00 | Hereditary nephropathy not elsewhere classified |
| K0A5000 | Hereditary nephropathy NEC, minor glomerular abnormality |
| K0A5100 | Hereditary nephropathy NEC,focal+segmnt glomerular lesion |
| K0A5200 | Hereditry nephropathy NEC,difus membran glomerulnephritis |
| K0A5300 | Heredtry nephrpthy NEC difus mesangial prolif glomnephrit |
| K0A5400 | Heredtry nephrpthy NEC difus endocapil prolif glomnephrit |
| K0A5500 | [X]Heredtry nephrpthy NEC difus mesangiocapilry glomneph |
| K0A5600 | Hereditary nephropathy, NEC, dense deposit disease |
| K0A5700 | Hereditary nephropathy,NEC,difus crescentic glomnephritis |
| K0A5X00 | Hereditary nephropathy, unspecif morphological changes |
| K0A6.00 | Glomerular disorders in neoplastic diseases |
| K0A8.00 | Rapidly progressive glomerulonephritis |
| K0A9.00 | Cytomegalovirus-induced glomerulonephritis |
| K0B..00 | Renal tubulo-interstitial disorders in diseases EC |
| K0B0.00 | Ren tubulo-interstital disord infect and parasitic dis EC |
| K0B1.00 | Renal tubulo-interstitial disorder/ neoplastic diseases |
| K0B2.00 | Ren tub-interst disordr/blood dis+disordr inv immune mech |
| K0B3.00 | Renal tubulo-interstitial disorders in metabolic diseases |
| K0B4.00 | Ren tub-interstitl disordr/systemc connectv tiss disorder |
| K0B4000 | Renal tubulo-interstitial disorder in SLE |
| K0B5.00 | Renal tubulo-interstitial disordrs in transplant rejectn |
| K0B6.00 | Balkan nephropathy |
| K0C..00 | Drug/heavy-metal-induced tubulo-interstitial and tub conditn |
| K0C0.00 | Analgesic nephropathy |
| K0C1.00 | Nephropathy induced by other drugs meds and biologl substncs |
| K0C2.00 | Nephropathy induced by unspec drug medicament or biol subs |
| K0C3.00 | Nephropathy induced by heavy metals |
| K0C3400 | Chronic interstitial nephritis due to heavy metals |
| K0C3500 | Chronic lead nephropathy |
| K0C3600 | Chronic mercury nephropathy |
| K0C3700 | Chronic cadmium nephropathy |
| K0C3800 | Saturnine nephropathy |
| K0C4.00 | Toxic nephropathy, not elsewhere classified |
| K0C6.00 | Chronic lithium nephrotoxicity |
| K0D..00 | End-stage renal disease |
| K0E..00 | Acute-on-chronic renal failure |
| K0G..00 | Sickle cell nephropathy |
| K0J..00 | Renal disorders in systemic disease |
| K0J0.00 | Renal involvement in scleroderma |
| K0J1.00 | Renal involvement in malignant disease |
| K0y..00 | Other specified nephritis, nephrosis or nephrotic syndrome |
| K0y1.00 | Acquired magnesium-losing nephropathy |
| K0z..00 | Nephritis, nephrosis and nephrotic syndrome NOS |
| K132.11 | Acquired renal cystic disease |
| K138600 | Renal vascular disease |
| K13C.00 | Chronic drug-induced renal disease |
| K13yB00 | Ischaemic nephropathy |
| K13z.00 | Kidney and ureter disease NOS |
| K196.11 | Obstructive uropathy, unspecified |
| K19C.00 | Other obstructive and reflux uropathy |
| K19X.00 | Obstructive and reflux uropathy, unspecified |
| Kyu0.00 | [X]Glomerular diseases |
| Kyu0000 | [X]Glomerular disorders in infectious+parasitic diseases CE |
| Kyu0100 | [X]Glomerular disorders in neoplastic diseases CE |
| Kyu0200 | [X]Glomerulr disordrs/bld dis+disordr inv immune mechansm CE |
| Kyu0300 | [X]Glomerular disorders in diabetes mellitus |
| Kyu0400 | [X]Glomerulr disordr/oth endocrine,nutritnl+metabolic dis CE |
| Kyu0500 | [X]Glomerular disordrs/systemic disordrs/connectiv tissue CE |
| Kyu0600 | [X]Glomerular disorders in other diseases CE |
| Kyu0700 | [X]Rapidly progressive nephritic syndrome, other |
| Kyu0800 | [X]Unspecif nephritic syndr, minor glomerular abnormality |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| Kyu0900 | [X]Unsp nephrit synd, diff mesang prolif glomerulonephritis |
| Kyu0A00 | [X]Unsp nephrit synd, diff endocap prolif glomerulonephritis |
| Kyu0B00 | [X]Unspecified nephritic syndrome, dense deposit disease |
| Kyu0C00 | [X]Unspecif nephr synd, diff concentric glomerulonephritis |
| Kyu0F00 | [X]Hereditary nephropathy, unspecif morphological changes |
| Kyu1.00 | [X]Renal tubulo-interstitial diseases |
| Kyu1000 | [X]Other chronic tubulo-interstitial nephritis |
| Kyu1100 | [X]Other and unspecified hydronephrosis |
| Kyu1200 | [X]Other obstructive and reflux uropathy |
| Kyu1300 | [X]Obstructive and reflux uropathy, unspecified |
| Kyu1400 | [X]Nephropathy induced by other drugs+biological substances |
| Kyu1500 | [X]Toxic nephropathy, not elsewhere classified |
| Kyu1600 | [X]Other specified renal tubulo-interstitial diseases |
| Kyu1700 | [X]Renal tubulo-interstitial disordr/infect+parasitic dis CE |
| Kyu1800 | [X]Renal tubulo-interstitial disordrs/neoplastic diseases CE |
| Kyu1900 | [X]Renal tub-interstl disord/bld dis+disord invl imm mech CE |
| Kyu1A00 | [X]Renal tubulo-interstitial disorders/metabolic diseases CE |
| Kyu1B00 | [X]Renal tubul-interstitl disordrs/connectv tissu disordr CE |
| Kyu1C00 | [X]Renal tubulo-interstitial disorders/transplant rejection |
| Kyu1D00 | [X]Renal tubulo-interstitial disorders in other diseases CE |
| Kyu1E00 | [X]Tubulo-interstit nephritis, not specif as acute or chron |
| Kyu2.00 | [X]Renal failure |
| Kyu2100 | [X]Other chronic renal failure |
| Kyu4000 | [X]Other disorders resulting/impaired renal tubular function |
| Kyu4200 | [X]Oth disordrs/kidney+ureter/infects+parasitic diseases CE |
| Kyu4300 | [X]Other disorders of kidney+ureter in other diseases CE |
| L093300 | Renal tubular necrosis following abortive pregnancy |
| L162.00 | Unspecified renal disease in pregnancy |
| L162.12 | Nephropathy NOS in pregnancy without hypertension |
| L162000 | Unspecified renal disease in pregnancy unspecified |
| L162100 | Unspecified renal disease in pregnancy - delivered |
| L162200 | Unspecified renal disease in pregnancy - del with p/n comp |
| L162300 | Unspecified renal disease in pregnancy - not delivered |
| L162400 | Unspecified renal disease in pregnancy with p/n complication |
| L162z00 | Unspecified renal disease in pregnancy NOS |
| PD00200 | Unilat renal agenesis with contralat hypoplasia/dysplasia |
| PD03.00 | Hypoplasia of kidney |
| PD03000 | Bilateral renal hypoplasia |
| PD03100 | Unilateral renal hypoplasia |
| PD03200 | Segmental renal hypoplasia |
| PD04.00 | Dysplasia of kidney |
| PD04000 | Bilateral renal dysplasia |
| PD04100 | Unilateral renal dysplasia |
| PD04200 | Renal dysplasia and retinal aplasia |
| PD04z00 | Dysplasia of kidney NOS |
| PD1..00 | Congenital cystic kidney disease |
| PD1..11 | Congenital cystic renal disease |
| PD1..12 | Fibrocystic kidney |
| PD1..13 | Polycystic kidney |
| PD1..14 | Sponge kidney |
| PD11.00 | Polycystic kidney disease |
| PD11000 | Polycystic kidneys, infantile type |
| PD11011 | Autosomal recessive polycystic kidney disease |
| PD11100 | Polycystic kidneys, adult type |
| PD11111 | Autosomal dominant polycystic kidney disease |
| PD11z00 | Polycystic kidney disease NOS |
| PD11z11 | Cystic kidney disease NEC |
| PD12.00 | Medullary cystic disease |
| PD12000 | Medullary cystic disease, juvenile type |
| PD12011 | Nephronophthisis |
| PD12012 | Autosomal recessive medullary cystic disease |
| PD12100 | Medullary cystic disease, adult type |
| PD12111 | Medullary sponge kidney |
| PD12200 | Nephronophthisis - medullary cystic disease |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| PD12211 | Autosomal dominant medullary cystic disease |
| PD12y00 | Medullary cystic disease OS |
| PD12z00 | Medullary cystic disease NOS |
| PD13.00 | Multicystic renal dysplasia |
| PD13.11 | Multicystic kidney |
| PD1y.00 | Other specified congenital cystic kidney disease |
| PD1y000 | Fibrocystic kidney disease |
| PD1y011 | Fibrocystic renal degeneration |
| PD1y100 | Cortical cystic disease |
| PD1yz00 | Other congenital cystic kidney disease NOS |
| PD1z.00 | Congenital cystic kidney disease NOS |
| PD39.00 | Hyperplasia of kidney |
| PD8..00 | Congenital abnormality of the kidney |
| PD80.00 | Duplex kidney |
| PKy5E00 | Branchio-otorenal dysplasia |
| Pyu7000 | [X]Other cystic kidney diseases |
| Q48y000 | Congenital renal failure |
| SK05.00 | Renal failure following crush syndrome |
| SK05.11 | Renal failure after crushing |
| SP01500 | Mechanical complication of dialysis catheter |
| SP05613 | [X] Peritoneal dialysis associated peritonitis |
| SP06B00 | Continuous ambulatory peritoneal dialysis associated perit |
| SP07G00 | Stenosis of arteriovenous dialysis fistula |
| SP08300 | Kidney transplant failure and rejection |
| SP08C00 | Accelerated rejection of renal transplant |
| SP08D00 | Acute-on-chronic rejection of renal transplant |
| SP08E00 | Acute rejection of renal transplant - grade I |
| SP08F00 | Acute rejection of renal transplant - grade II |
| SP08G00 | Acute rejection of renal transplant - grade III |
| SP08H00 | Acute rejection of renal transplant |
| SP08J00 | Chronic rejection of renal transplant |
| SP08J11 | Chronic transplant nephropathy |
| SP08K00 | Chronic rejection of renal transplant - grade 1 |
| SP08L00 | Chronic rejection of renal transplant - grade II |
| SP08M00 | Chronic rejection of renal transplant - grade III |
| SP08N00 | Unexplained episode of renal transplant dysfunction |
| SP08P00 | Stenosis of vein of transplanted kidney |
| SP08Q00 | Aneurysm of artery of transplanted kidney |
| SP08R00 | Renal transplant rejection |
| SP08S00 | Aneurysm of vein of transplanted kidney |
| SP08T00 | Urological complication of renal transplant |
| SP08V00 | Very mild acute rejection of renal transplant |
| SP08W00 | Vascular complication of renal transplant |
| SP08X00 | Rupture of artery of transplanted kidney |
| SP08Y00 | Rupture of vein of transplanted kidney |
| SP08Z00 | Thrombosis of artery of transplanted kidney |
| SP08a00 | Thrombosis of vein of transplanted kidney |
| SP08b00 | De novo glomerulonephritis |
| SP0E.00 | Disorders associated with peritoneal dialysis |
| SP0E000 | Bloodstained peritoneal dialysis effluent |
| SP0E100 | Thrombus in peritoneal dialysis catheter |
| SP0F.00 | Haemodialysis first use syndrome |
| SP0G.00 | Anaphylactoid reaction due to haemodialysis |
| SP0H.00 | Disorder associated with dialysis |
| SP0H000 | Dialysis disequilibrium |
| SP15400 | Renal failure as a complication of care |
| SP15411 | Kidney failure as a complication of care |
| SP15412 | Post operative renal failure |
| SP3y900 | Acute hypercalcaemia of dialysis |
| TA02.00 | Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion |
| TA02000 | Accid cut,puncture,perf,h'ge - kidney dialysis |
| TA02011 | Accidental cut/puncture/perf/haem'ge during renal dialysis |
| TA12000 | Foreign object left in body during kidney dialysis |
| TA12011 | Foreign object left in body during renal dialysis |

**Table G.5** Continued.

| Read code | Code description |
|---|---|
| TA22000 | Failure of sterile precautions during kidney dialysis |
| TA22011 | Failure of sterile precautions during renal dialysis |
| TA42000 | Mechanical failure of apparatus during kidney dialysis |
| TA42011 | Mechanical failure of apparatus during renal dialysis |
| TB00100 | Kidney transplant with complication, without blame |
| TB00111 | Renal transplant with complication, without blame |
| TB11.00 | Kidney dialysis with complication, without blame |
| TB11.11 | Renal dialysis with complication, without blame |
| U612200 | [X]Failure sterile precautions dur kidney dialys/other perf |
| U641.00 | [X]Kidny dialysis caus abn reac pt/lat comp no misad at time |
| Z1A..00 | Dialysis training |
| Z1A1.00 | Peritoneal dialysis training |
| Z1A1.11 | PD - Peritoneal dialysis training |
| Z1A2.00 | Haemodialysis training |
| Z1A2.11 | HD - Haemodialysis training |
| Z919.00 | Care of haemodialysis equipment |
| Z919100 | Priming haemodialysis lines |
| Z919200 | Washing back through haemodialysis lines |
| Z919300 | Reversing haemodialysis lines |
| Z919400 | Recirculation of the dialysis machine |
| Z91A.00 | Peritoneal dialysis bag procedure |
| Z91A100 | Putting additive into peritoneal dialysis bag |
| ZC2CL11 | Dietary advice kidney disease |
| ZV42000 | [V]Kidney transplanted |
| ZV45100 | [V]Renal dialysis status |
| ZV56.00 | [V]Aftercare involving intermittent dialysis |
| ZV56000 | [V]Aftercare involving extracorporeal dialysis |
| ZV56011 | [V]Aftercare involving renal dialysis NOS |
| ZV56100 | [V]Preparatory care for dialysis |
| ZV56y00 | [V]Other specified aftercare involving intermittent dialysis |
| ZV56y11 | [V]Aftercare involving peritoneal dialysis |
| ZV56z00 | [V]Unspecified aftercare involving intermittent dialysis |
| ZVu3G00 | [X]Other dialysis |

**Table G.6** Read codes related to conditions associated with gastrointestinal malabsorption.

| Read code | Code description |
|---|---|
| 13YB.00 | Coeliac UK member |
| 14CH.00 | History of chronic pancreatitis |
| 6648.00 | Coeliac disease monitoring |
| 6648000 | Coeliac disease annual review |
| 66k..00 | Cystic fibrosis monitoring |
| 66k0.00 | Cystic fibrosis annual review |
| 7Q09600 | Total parenteral nutrition |
| 8CA4W00 | Dietary education for inflammatory bowel disease |
| 8Cc5.00 | Management of inflammatory bowel disease |
| 8Cc5.11 | Management of IBD (inflammatory bowel disease) |
| 8IAp.00 | Coeliac disease annual review declined |
| 9Ngq.00 | On parenteral nutrition |
| 9No7.00 | Seen in cystic fibrosis clinic |
| 9mB..00 | Coeliac disease monitoring invitation |
| 9mB0.00 | Coeliac disease monitoring telephone invitation |
| 9mB1.00 | Coeliac disease monitoring invitation first letter |
| 9mB2.00 | Coeliac disease monitoring invitation second letter |
| 9mB3.00 | Coeliac disease monitoring invitation third letter |
| C10N100 | Cystic fibrosis related diabetes mellitus |
| C370.00 | Cystic fibrosis |
| C370000 | Cystic fibrosis with no meconium ileus |
| C370100 | Cystic fibrosis with meconium ileus |
| C370111 | Meconium ileus in cystic fibrosis |
| C370200 | Cystic fibrosis with pulmonary manifestations |
| C370300 | Cystic fibrosis with intestinal manifestations |
| C370400 | Arthropathy in cystic fibrosis |
| C370500 | Cystic fibrosis with distal intestinal obstruction syndrome |
| C370700 | Liver disease due to cystic fibrosis |
| C370800 | Cystic fibrosis related cirrhosis |
| C370900 | Exacerbation of cystic fibrosis |
| C370y00 | Cystic fibrosis with other manifestations |
| C370y11 | Cystic fibrosis with combined manifestations |
| C370z00 | Cystic fibrosis NOS |
| J08z900 | Orofacial Crohn's disease |
| J4...12 | Inflammatory bowel disease |
| J40..00 | Regional enteritis - Crohn's disease |
| J40..11 | Crohn's disease |
| J400200 | Crohn's disease of the terminal ileum |
| J400300 | Crohn's disease of the ileum unspecified |
| J400400 | Crohn's disease of the ileum NOS |
| J400500 | Exacerbation of Crohn's disease of small intestine |
| J400z00 | Crohn's disease of the small bowel NOS |
| J401200 | Exacerbation of Crohn's disease of large intestine |
| J401z00 | Crohn's disease of the large bowel NOS |
| J401z11 | Crohn's colitis |
| J40z.11 | Crohn's disease NOS |
| J41..12 | Ulcerative colitis and/or proctitis |
| J410.00 | Ulcerative proctocolitis |
| J410000 | Ulcerative ileocolitis |
| J410100 | Ulcerative colitis |
| J410200 | Ulcerative rectosigmoiditis |
| J410300 | Ulcerative proctitis |
| J410400 | Exacerbation of ulcerative colitis |
| J410z00 | Ulcerative proctocolitis NOS |
| J411.00 | Ulcerative (chronic) enterocolitis |
| J412.00 | Ulcerative (chronic) ileocolitis |
| J413.00 | Ulcerative pancolitis |
| J671.00 | Chronic pancreatitis |
| J671000 | Alcohol-induced chronic pancreatitis |
| J671100 | Gallstone chronic pancreatitis |
| J67y500 | Pancreatic insufficiency |
| J67y600 | Exocrine pancreatic insufficiency |

**Table G.6** Continued.

| Read code | Code description |
|---|---|
| J69..00 | Intestinal malabsorption |
| J690.00 | Coeliac disease |
| J690.11 | Coeliac rickets |
| J690.12 | Gee - Herter disease |
| J690.13 | Gluten enteropathy |
| J690.14 | Sprue - nontropical |
| J690.16 | Villous atrophy |
| J690.17 | Partial villous atrophy |
| J690000 | Congenital coeliac disease |
| J690100 | Acquired coeliac disease |
| J690z00 | Coeliac disease NOS |
| J691.00 | Tropical sprue |
| J692.00 | Blind loop syndrome |
| J693.00 | Other postsurgical nonabsorption |
| J693.11 | Postsurgical malabsorption - other |
| J693000 | Post gastrointestinal tract surgery hypoglycaemia |
| J693100 | Post gastrointestinal tract surgery malnutrition |
| J693z00 | Postsurgical nonabsorption NOS |
| J694.00 | Pancreatic steatorrhoea |
| J69y.00 | Other intestinal malabsorption |
| J69y000 | Chronic steatorrhoea |
| J69y011 | Malabsorption due to intolerance to fat |
| J69y200 | Intestinal malabsorption of protein |
| J69y600 | Intestinal malabsorption of fat |
| J69yz00 | Other gastrointestinal tract malabsorption NOS |
| J69yz13 | Malabsorption syndrome NOS |
| J69z.00 | Intestinal malabsorption NOS |
| Jyu4000 | [X]Other Crohn's disease |
| Jyu4100 | [X]Other ulcerative colitis |
| Jyu8400 | [X]Other chronic pancreatitis |
| Jyu9000 | [X]Other intestinal malabsorption |
| N031000 | Arthropathy in ulcerative colitis |
| N031100 | Arthropathy in Crohn's disease |
| N045300 | Juvenile arthritis in Crohn's disease |
| N045400 | Juvenile arthritis in ulcerative colitis |
| PB5z.12 | Short bowel syndrome |
| PJ53500 | Shwachman-Diamond syndrome |
| ZC2C200 | Dietary advice for coeliac disease |
| ZC32.49 | TPN - Total parenteral nutrition |
| ZC64.00 | Parenteral nutrition |
| ZC64.11 | Parenteral alimentation |
| ZC64.12 | IV - Intravenous feeding |
| ZC64.13 | Intravenous feeding |
| ZC64.14 | Parenteral feeding |
| ZC64.15 | PN - Parenteral nutrition |
| ZC64100 | Central line feeding |
| ZC64200 | Peripheral line feeding |
| ZC64300 | Total parenteral nutrition |
| ZC64311 | TPN - Total parenteral nutrition |
| ZR3S.00 | Crohn's disease activity index |
| ZR3S.11 | CDAI - Crohn's disease activity index |

## G.7 Identification of Read Codes Referring to Symptoms and Clinical Complications of Vitamin D Deficiency

### *G.7.1 Identification of Read Codes Related to Musculoskeletal and Non-Specific Pain*

The following truncated search terms were used to identify Read codes related to musculoskeletal and non-specific pain: ‘pain’, ‘ache’, ‘aching’, ‘arthralgia’, ‘arthropathy’, ‘cramp’, ‘cervicalgia’, ‘musculo’, ‘myalgia’. Common code stems were used to identify additional relevant codes. A total of 175 relevant codes were identified. The final list of included codes is shown in Table G.7.

**Table G.7** Read codes related to musculoskeletal and non-specific pain.

| Read code | Code description |
|---|---|
| 16C..00 | Backache symptom |
| 16C2.00 | Backache |
| 16C3.00 | Backache with radiation |
| 16C4.00 | Back pain worse on sneezing |
| 16C5.00 | C/O - low back pain |
| 16C6.00 | Back pain without radiation NOS |
| 16C7.00 | C/O - upper back ache |
| 16C9.00 | Chronic low back pain |
| 16CA.00 | Mechanical low back pain |
| 16CZ.00 | Backache symptom NOS |
| 16Z2.00 | Growing pains |
| 16Z2.11 | Growing pains symptom |
| 182B.00 | Rib pain |
| 182B000 | Costal margin chest pain |
| 182C.00 | Chest wall pain |
| 1D13.00 | C/O: a pain |
| 1D13.11 | Pain |
| 1D13.12 | C/O - an ache |
| 1D13000 | C/O - pain in toes |
| 1D13100 | C/O - pain in hallux |
| 1D13111 | C/O - pain in big toe |
| 1DC2.00 | Aching pain |
| 1DC8.00 | Generalised pain [symptom] |
| 1DCC.00 | Aching muscles |
| 1M0..00 | Pain in upper limb |
| 1M00.00 | Pain in elbow |
| 1M00.11 | Elbow pain |
| 1M01.00 | Pain in wrist |
| 1M1..00 | Pain in lower limb |
| 1M10.00 | Knee pain |
| 1M11.00 | Foot pain |
| 1M12.00 | Anterior knee pain |
| 1M13.00 | Ankle pain |
| N065.00 | Unspecified polyarthropathy or polyarthritis |
| N065.11 | Polyarthropathy NEC |
| N065000 | Unspecified polyarthropathy of unspecified site |
| N065100 | Unspecified polyarthropathy of the shoulder region |
| N065200 | Unspecified polyarthropathy of the upper arm |
| N065300 | Unspecified polyarthropathy of the forearm |
| N065400 | Unspecified polyarthropathy of the hand |
| N065500 | Unspecified polyarthropathy of the pelvic region and thigh |
| N065600 | Unspecified polyarthropathy of the lower leg |
| N065700 | Unspecified polyarthropathy of the ankle and foot |
| N065800 | Unspecified polyarthropathy of other specified site |
| N065900 | Unspecified polyarthropathy of multiple sites |

**Table G.7** Continued.

| Read code | Code description |
|---|---|
| N065z00 | Unspecified polyarthropathy or polyarthritis NOS |
| N06y.00 | Other specified arthropathy |
| N06y000 | Other specified arthropathy of unspecified site |
| N06y100 | Other specified arthropathy of the shoulder region |
| N06y200 | Other specified arthropathy of the upper arm |
| N06y300 | Other specified arthropathy of the forearm |
| N06y400 | Other specified arthropathy of the hand |
| N06y500 | Other specified arthropathy of the pelvic region and thigh |
| N06y600 | Other specified arthropathy of the lower leg |
| N06y700 | Other specified arthropathy of the ankle and foot |
| N06y800 | Other specified arthropathy of other specified site |
| N06y900 | Other specified arthropathy of multiple sites |
| N06yz00 | Other specified arthropathy NOS |
| N06z.00 | Arthropathy NOS |
| N06z000 | Arthropathy NOS, of unspecified site |
| N06z100 | Arthropathy NOS, of the shoulder region |
| N06z200 | Arthropathy NOS, of the upper arm |
| N06z300 | Arthropathy NOS, of the forearm |
| N06z400 | Arthropathy NOS, of the hand |
| N06z500 | Arthropathy NOS, of the pelvic region and thigh |
| N06z600 | Arthropathy NOS, of the lower leg |
| N06z700 | Arthropathy NOS, of the ankle and foot |
| N06z800 | Arthropathy NOS, of other specified site |
| N06z900 | Arthropathy NOS, of multiple sites |
| N06zz00 | Arthropathy NOS |
| N094.00 | Pain in joint - arthralgia |
| N094.11 | Ache in joint |
| N094000 | Arthralgia of unspecified site |
| N094100 | Arthralgia of the shoulder region |
| N094111 | Shoulder joint pain |
| N094200 | Arthralgia of the upper arm |
| N094211 | Elbow joint pain |
| N094300 | Arthralgia of the forearm |
| N094311 | Wrist joint pain |
| N094400 | Arthralgia of the hand |
| N094411 | Hand joint pain |
| N094500 | Arthralgia of the pelvic region and thigh |
| N094511 | Coxalgia |
| N094512 | Hip joint pain |
| N094600 | Arthralgia of the lower leg |
| N094611 | Knee joint pain |
| N094700 | Arthralgia of the ankle and foot |
| N094711 | Ankle joint pain |
| N094800 | Arthralgia of other specified site |
| N094900 | Arthralgia of multiple joints |
| N094A00 | Arthralgia of shoulder |
| N094B00 | Arthralgia of sternoclavicular joint |
| N094C00 | Arthralgia of acromioclavicular joint |
| N094D00 | Arthralgia of elbow |
| N094D11 | Elbow joint pain |
| N094E00 | Arthralgia of distal radio-ulnar joint |
| N094F00 | Arthralgia of wrist |
| N094F11 | Wrist pain |
| N094G00 | Arthralgia of MCP joint |
| N094H00 | Arthralgia of PIP joint of finger |
| N094J00 | Arthralgia of DIP joint of finger |
| N094K00 | Arthralgia of hip |
| N094K11 | Coxalgia |
| N094K12 | Hip pain |
| N094L00 | Arthralgia of sacro-iliac joint |
| N094M00 | Arthralgia of knee |
| N094N00 | Arthralgia of tibio-fibular joint |
| N094P00 | Arthralgia of ankle |
| N094Q00 | Arthralgia of subtalar joint |

**Table G.7** Continued.

| Read code | Code description |
|---|---|
| N094R00 | Arthralgia of talonavicular joint |
| N094S00 | Arthralgia of other tarsal joint |
| N094T00 | Arthralgia of 1st MTP joint |
| N094U00 | Arthralgia of lesser MTP joint |
| N094V00 | Arthralgia of IP joint of toe |
| N094W00 | Anterior knee pain |
| N094z00 | Arthralgia NOS |
| N096.12 | Musculoskeletal pain - joints |
| N131.00 | Cervicalgia - pain in neck |
| N131.11 | Pain in cervical spine |
| N134.13 | Cervical root pain |
| N138.00 | Cervicalgia |
| N141.00 | Pain in thoracic spine |
| N141.11 | Acute back pain - thoracic |
| N142.00 | Pain in lumbar spine |
| N142.11 | Low back pain |
| N142.12 | Lumbalgia |
| N142.13 | Acute back pain - lumbar |
| N142.14 | Lumbago |
| N142000 | Lumbago with sciatica |
| N143.11 | Acute back pain with sciatica |
| N144011 | Thoracic nerve root pain |
| N145.00 | Backache, unspecified |
| N145.11 | Acute back pain - unspecified |
| N145.12 | Back pain, unspecified |
| N147211 | Pain in coccyx |
| N241.00 | Myalgia and myositis unspecified |
| N241000 | Myalgia unspecified |
| N241012 | Muscle pain |
| N241z00 | Myalgia or myositis NOS |
| N245.00 | Pain in limb |
| N245.11 | Ankle pain |
| N245.12 | Arm pain |
| N245.13 | Foot pain |
| N245.14 | Hand pain |
| N245.15 | Heel pain |
| N245.16 | Leg pain |
| N245.17 | Shoulder pain |
| N245.18 | Thigh pain |
| N245.19 | Pain in buttock |
| N245000 | Hand pain |
| N245011 | Thumb pain |
| N245012 | Finger pain |
| N245100 | Foot pain |
| N245111 | Toe pain |
| N245200 | Pain in leg |
| N245211 | Aching leg syndrome |
| N245300 | Pain in arm |
| N245400 | Calf pain |
| N245500 | Axillary pain |
| N245700 | Shoulder pain |
| N247.00 | Other musculoskeletal limb symptoms |
| N247100 | Leg cramps |
| N247111 | Night cramps |
| N247200 | Cramp |
| N247z00 | Musculoskeletal limb symptoms NOS |
| N247z11 | Hand cramps |
| N33A.00 | Bone pain |
| N33A000 | Bony pelvic pain |
| N33A100 | Clavicle pain |
| R00z200 | [D]Pain, generalized |
| R00z211 | [D]General aches and pains |
| R01..11 | [D]Musculoskeletal symptoms |
| R01z100 | [D]Growing pains - limbs |

**Table G.7** Continued.

| Read code | Code description |
|---|---|
| R01z200 | [D]Musculoskeletal pain |
| R065A00 | [D]Musculoskeletal chest pain |

### *G.7.2 Identification of Read Codes Related to Tiredness and Fatigue*

The following truncated search terms were used to identify Read codes related to tiredness and fatigue: ‘tired’, ‘letharg’, ‘malaise’, ‘fatigue’, ‘energy’, ‘asthenia’, ‘lassitude’. Common code stems were used to identify additional relevant codes. A total of 33 relevant codes were identified. The final list of included codes is shown in Table G.8.

**Table G.8** Read codes related to tiredness and fatigue.

| Read code | Code description |
|---|---|
| 168..00 | Tiredness symptom |
| 168..11 | Fatigue - symptom |
| 168..12 | Lethargy - symptom |
| 168..13 | Malaise - symptom |
| 1682.00 | Fatigue |
| 1683.00 | Tired all the time |
| 1683.11 | C/O - "tired all the time" |
| 1684.00 | Malaise/lethargy |
| 1684.11 | C/O - debility - malaise |
| 168Z.00 | Tiredness symptom NOS |
| E205.12 | Tired all the time |
| Eu46011 | [X]Fatigue syndrome |
| F286.00 | Chronic fatigue syndrome |
| F286.11 | CFS - Chronic fatigue syndrome |
| F286.12 | Postviral fatigue syndrome |
| F286.13 | PVFS - Postviral fatigue syn |
| F286.14 | Post-viral fatigue syndrome |
| F286.15 | Myalgic encephalomyelitis |
| F286.16 | ME - Myalgic encephalomyelitis |
| F286000 | Mild chronic fatigue syndrome |
| F286100 | Moderate chronic fatigue synd |
| F286200 | Severe chronic fatigue synd |
| R007.00 | [D]Malaise and fatigue |
| R007000 | [D]Malaise |
| R007100 | [D]Fatigue |
| R007200 | [D]Asthenia NOS |
| R007211 | [D]General weakness |
| R007300 | [D]Lethargy |
| R007400 | [D]Postviral (asthenic) syndrome |
| R007411 | [D]Post viral debility |
| R007500 | [D]Tiredness |
| R007z00 | [D]Malaise and fatigue NOS |
| R007z11 | [D]Lassitude |

### G.7.3 Identification of Read Codes Related to Skeletal Deformity

The following truncated search terms were used to identify Read codes related to skeletal deformity: ‘bow AND leg’, ‘bowed’, ‘bowing’, ‘genu’, ‘varum’, ‘varus’, ‘valgum’, ‘valgus’, ‘knock AND knee’, ‘deform’, ‘abnormal AND bone’, ‘abnormal AND leg’, ‘craniotab’, ‘ping AND pong’, ‘kypho’, ‘scolio’, ‘spine’, ‘spinal’, ‘rosary’, ‘ricket’, ‘rachit’, ‘bead’. Common code stems were used to identify additional relevant codes. A total of 93 relevant codes were identified. The final list of included codes is shown in Table G.9.

**Table G.9** Read codes related to skeletal deformity.

| Read code | Code description |
|---|---|
| 1D16.00 | C/O: a deformity |
| 2HA..00 | O/E - bone abnormal |
| 2HA..12 | O/E - leg bone abnormal |
| 2HA8.00 | O/E - thigh bone abnormal |
| 2HA9.00 | O/E - lower leg bone abnormal |
| 2HAZ.00 | O/E - bone abnormal NOS |
| 2HB..00 | O/E - bone abnormality |
| 2HB2.00 | O/E - bone deformed |
| 2HBZ.00 | O/E - bone abnormality NOS |
| 2I13.00 | O/E - a deformity |
| Nyu3400 | [X]Other specified acquired deformities of limbs |
| NyuE000 | [X]Oth specified acquired deformities/musculoskeletal system |
| N36..00 | Other acquired limb deformity |
| N364.00 | Acquired genu valgum and varum |
| N364000 | Acquired genu valgum |
| N364011 | Knock knee |
| N364100 | Acquired genu varum |
| N364111 | Bow legged |
| N364z00 | Acquired genu valgum or varum NOS |
| N365.00 | Genu recurvatum - acquired |
| N36y.00 | Acquired deformity of other limb parts |
| N36y.12 | Other deformity of bone |
| N36y200 | Deformity of bone |
| N36yC00 | Deformity of femur |
| N36yE00 | Deformity of tibia |
| N36yF00 | Deformity of fibula |
| N36yz00 | Acquired limb deformity NEC |
| N36z.00 | Acquired limb deformity NOS |
| N38..00 | Other acquired deformity |
| N38y.00 | Other acquired deformity |
| N38yz00 | Other acquired deformity NOS |
| N38z.00 | Acquired deformity NOS |
| PE4..00 | Genu recurvatum and long leg bone bowing |
| PE4..11 | Congenital leg bone bowing |
| PE40.00 | Congenital genu recurvatum |
| PE42.00 | Congenital bowing of femur |
| PE43.00 | Congenital bowing of tibia and fibula |
| PE43000 | Congenital bowing of tibia |
| PE43100 | Congenital bowing of fibula |
| PE44.00 | Congenital bowing of long leg bone, unspecified |
| PE44.11 | Bow legs NOS |
| PE4z.00 | Genu recurvatum and long leg bone bowing NOS |
| PE9..00 | Other musc skeletal deformity |
| PE9..11 | Other congenital musculoskeletal deformity |
| PEz..00 | Congenital musculoskeletal deformity NOS |
| PF64100 | Congenital genu valgum - knock-knee |
| PF64200 | Congenital genu varum - bowleg |
| Q48y411 | Neonatal "craniotabes" |
| 2374.00 | O/E - rickety rosary |

**Table G.9** Continued.

| Read code | Code description |
|---|---|
| 2376.00 | O/E - kyphoscoliotic chest def |
| 2H8..00 | O/E - spine abnormal |
| 2H82.00 | O/E - cervical spine abnormal |
| 2H83.00 | O/E - thoracic spine abnormal |
| 2H84.00 | O/E - lumbar spine abnormal |
| 2H8Z.00 | O/E - spine abnormal NOS |
| Nyu5000 | [X]Other secondary kyphosis |
| Nyu5100 | [X]Other and unspecified kyphosis |
| Nyu5300 | [X]Other idiopathic scoliosis |
| Nyu5400 | [X]Other secondary scoliosis |
| Nyu5500 | [X]Other forms of scoliosis |
| N37..00 | Curvature of spine |
| N370.00 | Adolescent postural kyphosis |
| N371.00 | Acquired kyphosis |
| N371000 | Acquired postural kyphosis |
| N371z00 | Acquired kyphosis NOS |
| N373.00 | Kyphoscoliosis and scoliosis |
| N373000 | Idiopathic scoliosis |
| N373100 | Idiopathic kyphoscoliosis |
| N373200 | Resolving infantile idiopathic scoliosis |
| N373300 | Progressive infantile idiopathic scoliosis |
| N373500 | Thoracogenic scoliosis |
| N373600 | Postural scoliosis |
| N373700 | Adolescent idiopathic scoliosis |
| N373z00 | Kyphoscoliosis or scoliosis NOS |
| N374.00 | Curvature of spine associated with other conditions |
| N374.11 | Kyphosis, scoliosis, and lordosis associated with oth cond |
| N374000 | Curvature of spine, unspecified |
| N374100 | Kyphosis associated with other condition |
| N374300 | Scoliosis associated with other condition |
| N374X00 | Other and unspecified kyphosis |
| N374z00 | Curvature of spine associated with other conditions NOS |
| N37y.00 | Other curvatures of spine |
| N37z.00 | Curvature of spine NOS |
| N37zz00 | Curvature of spine NOS |
| N385.00 | Acquired deformity of spine NOS |
| PE2..00 | Congenital spine deformity |
| PE20.00 | Congenital spine deformity, unspecified |
| PE22.00 | Congenital postural scoliosis |
| PE23.00 | Congenital scoliosis due to congenital bony malformation |
| PE2z.00 | Congenital spine deformity NOS |
| PE2z.11 | Congenital postural curvature of spine NOS |
| PG18.00 | Congenital kyphosis |
| PG18.11 | Congenital kyphoscoliosis |

### *G.7.4 Identification of Read Codes Related to Bone Fracture*

The following truncated search term was used to identify Read codes related to bone fracture: ‘fracture’. Common code stems were used to identify additional relevant codes. A total of 1,560 relevant codes were identified. The final list of included codes is shown in Table G.10.

**Table G.10** Read codes related to bone fracture.

| Read code | Code description |
|---|---|
| N331.00 | Pathological fracture |
| N331.13 | Sponanteous fracture |
| N331000 | Pathological fracture of thoracic vertebra |
| N331100 | Pathological fracture of lumbar vertebra |
| N331200 | Postoophorectomy osteoporosis with pathological fracture |
| N331300 | Osteoporosis of disuse with pathological fracture |
| N331400 | Postsurgical malabsorption osteoporosis with path fracture |
| N331500 | Drug-induced osteoporosis with pathological fracture |
| N331600 | Idiopathic osteoporosis with pathological fracture |
| N331700 | Fracture of bone in neoplastic disease |
| N331800 | Osteoporosis + pathological fracture lumbar vertebrae |
| N331900 | Osteoporosis + pathological fracture thoracic vertebrae |
| N331A00 | Osteoporosis + pathological fracture cervical vertebrae |
| N331B00 | Postmenopausal osteoporosis with pathological fracture |
| N331C00 | Pathological fracture of cervical vertebra |
| N331M00 | Fragility fracture due to unspecified osteoporosis |
| N331M11 | Minimal trauma fracture due to unspecified osteoporosis |
| N331N00 | Fragility fracture |
| N331N11 | Minimal trauma fracture |
| N331y00 | Other specified pathological fracture |
| N331z00 | Pathological fracture NOS |
| Q202.00 | Fracture of clavicle due to birth trauma |
| Q203.11 | Other fractures due to birth trauma |
| Q203.12 | Other birth fracture |
| Q203000 | Fracture of humerus due to birth trauma |
| Q203100 | Fracture of radius or ulna due to birth trauma |
| Q203111 | Birth fracture of radius |
| Q203112 | Birth fracture of ulna |
| Q203200 | Fracture of femur due to birth trauma |
| Q203300 | Fracture of tibia or fibula due to birth trauma |
| Q203400 | Fracture of skull due to birth trauma |
| Q203y11 | Fracture due to birth trauma NEC |
| Q203y12 | Fracture of nose due to birth trauma |
| Q204100 | Spine fracture due to birth trauma |
| S0...00 | Fracture of skull |
| S00..00 | Fracture of vault of skull |
| S00..11 | Frontal bone fracture |
| S00..12 | Parietal bone fracture |
| S000.00 | Closed fracture vault of skull without intracranial injury |
| S000000 | Closed #skull vlt no intracranial injury, unspec state consc |
| S000100 | Closed #skull vlt no intracranial injury, no loss of consc |
| S000200 | Closed #skull vlt no intracranial injury, <1hr loss of consc |
| S000300 | Closed #skull vlt no intracranial injury, 1-24hr loss consc |
| S000400 | Closed #skull vlt no intracranial injury, >24hr LOC+recovery |
| S000500 | Closed #skull vlt no intracranial inj,>24hr LOC not restored |
| S000600 | Closed #skull vlt no intracranial inj, LOC unspec duration |
| S000z00 | Closed #skull vlt no intracranial injury + concussion unspec |
| S001.00 | Closed fracture vault of skull with intracranial injury |
| S001000 | Closed #skull vlt + intracranial injury, unspec state consc |
| S001100 | Closed #skull vlt + intracranial injury, no loss of consc |
| S001200 | Closed #skull vlt + intracranial injury, <1hr loss of consc |
| S001300 | Closed #skull vlt + intracranial injury, 1-24hr loss consc |
| S001400 | Closed #skull vlt + intracranial injury, >24hr LOC+recovery |
| S001500 | Closed #skull vlt + intracranial inj, >24hr LOC not restored |
| S001600 | Closed #skull vlt + intracranial injury, LOC unspec duration |
| S001z00 | Closed #skull vlt with intracranial injury+concussion unspec |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S002.00 | Open fracture vault of skull without intracranial injury |
| S002000 | Open #skull vlt no intracranial injury, unspec state consc |
| S002100 | Open #skull vlt no intracranial injury, no loss of consc |
| S002200 | Open #skull vlt no intracranial injury, <1hr loss of consc |
| S002300 | Open #skull vlt no intracranial injury, 1-24hr loss of consc |
| S002400 | Open #skull vlt no intracranial injury, >24hr LOC+recovery |
| S002500 | Open #skull vlt no intracranial inj, >24hr LOC not restored |
| S002600 | Open #skull vlt no intracranial injury, LOC unspec duration |
| S002z00 | Open #skull vlt no intracranial injury + concussion unspec |
| S003.00 | Open fracture vault of skull with intracranial injury |
| S003000 | Open #skull vlt + intracranial injury, unspec state of consc |
| S003100 | Open #skull vlt + intracranial injury, no loss of consc |
| S003200 | Open #skull vlt + intracranial injury, <1hr loss of consc |
| S003300 | Open #skull vlt + intracranial injury, 1-24hr loss of consc |
| S003400 | Open #skull vlt + intracranial injury, >24hr LOC + recovery |
| S003500 | Open #skull vlt + intracranial inj, >24hr LOC not restored |
| S003600 | Open #skull vlt + intracranial injury, LOC unspec duration |
| S003z00 | Open #skull vlt with intracranial injury + concussion unspec |
| S00z.00 | Fracture of vault of skull NOS |
| S01..00 | Fracture of base of skull |
| S01..11 | Anterior fossa fracture |
| S01..12 | Ethmoid sinus fracture |
| S01..13 | Frontal sinus fracture |
| S01..14 | Middle fossa fracture |
| S01..15 | Occiput bone fracture |
| S01..16 | Orbital roof fracture |
| S01..17 | Posterior fossa fracture |
| S01..18 | Sphenoid bone fracture |
| S01..19 | Temporal bone fracture |
| S010.00 | Closed fracture base of skull without intracranial injury |
| S010000 | Closed #skull bse no intracranial injury, unspec state consc |
| S010100 | Closed #skull bse no intracranial injury, no loss of consc |
| S010200 | Closed #skull bse no intracranial injury, <1hr loss of consc |
| S010300 | Closed #skull bse no intracranial injury, 1-24hr loss consc |
| S010400 | Closed #skull bse no intracranial injury, >24hr LOC+recovery |
| S010500 | Closed #skull bse no intracranial inj,>24hr LOC not restored |
| S010600 | Closed #skull bse no intracranial inj, LOC unspec duration |
| S010z00 | Closed #skull bse no intracranial injury + concussion unspec |
| S011.00 | Closed fracture base of skull with intracranial injury |
| S011000 | Closed #skull bse + intracranial inj, unspec state of consc |
| S011100 | Closed #skull bse + intracranial injury, no loss of consc |
| S011200 | Closed #skull bse + intracranial injury, <1hr loss of consc |
| S011300 | Closed #skull bse + intracranial injury, 1-24hr loss consc |
| S011400 | Closed #skull bse + intracranial injury, >24hr LOC+recovery |
| S011500 | Closed #skull bse + intracranial inj, >24hr LOC not restored |
| S011600 | Closed #skull bse + intracranial injury, LOC unspec duration |
| S011z00 | Closed #skull bse + intracranial injury + concussion unspec |
| S012.00 | Open fracture base skull without mention intracranial injury |
| S012000 | Open #skull bse no intracranial inj, unspec state of consc |
| S012100 | Open #skull bse no intracranial injury, no loss of consc |
| S012200 | Open #skull bse no intracranial injury, <1hr loss of consc |
| S012300 | Open #skull bse no intracranial injury, 1-24hr loss of consc |
| S012400 | Open #skull bse no intracranial injury, >24hr LOC+recovery |
| S012500 | Open #skull bse no intracranial inj, >24hr LOC not restored |
| S012600 | Open #skull bse no intracranial injury, LOC unspec duration |
| S012z00 | Open #skull bse no intracranial injury + concussion unspec |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S013.00 | Open fracture base of skull with intracranial injury |
| S013000 | Open #skull bse + intracranial injury, unspec state of consc |
| S013100 | Open #skull bse + intracranial injury, no loss of consc |
| S013200 | Open #skull bse + intracranial injury, <1hr loss of consc |
| S013300 | Open #skull bse + intracranial injury, 1-24hr loss of consc |
| S013400 | Open #skull bse + intracranial injury, >24hr LOC + recovery |
| S013500 | Open #skull bse + intracranial inj, >24hr LOC not restored |
| S013600 | Open #skull bse + intracranial injury, LOC unspec duration |
| S013z00 | Open #skull bse + intracranial injury + concussion unspec |
| S01z.00 | Fracture of base of skull NOS |
| S02..00 | Fracture of face bones |
| S020.00 | Closed fracture nose |
| S020.11 | Closed fracture nasal bone |
| S021.00 | Open fracture nose |
| S021.11 | Open fracture nasal bone |
| S022.00 | Fracture of mandible, closed |
| S022.11 | Fracture of inferior maxilla, closed |
| S022.12 | Fracture of lower jaw, closed |
| S022000 | Closed fracture mandible (site unspecified) |
| S022100 | Closed fracture of mandible, condylar process |
| S022200 | Closed fracture of mandible, subcondylar |
| S022300 | Closed fracture of mandible, coronoid process |
| S022400 | Closed fracture of mandible, ramus, unspecified |
| S022500 | Closed fracture of mandible, angle of jaw |
| S022600 | Closed fracture of mandible, symphysis of body |
| S022700 | Closed fracture of mandible, alveolar border of body |
| S022800 | Closed fracture of mandible, body, other and unspecified |
| S022x00 | Closed fracture of mandible, multiple sites |
| S022z00 | Fracture of mandible, closed, NOS |
| S023.00 | Fracture of mandible, open |
| S023.11 | Fracture of lower jaw, open |
| S023000 | Open fracture mandible (site unspecified) |
| S023100 | Open fracture of mandible, condylar process |
| S023200 | Open fracture of mandible, subcondylar |
| S023300 | Open fracture of mandible, coronoid process |
| S023400 | Open fracture of mandible, ramus, unspecified |
| S023500 | Open fracture of mandible, angle of jaw |
| S023600 | Open fracture of mandible, symphysis of body |
| S023700 | Open fracture of mandible, alveolar border of body |
| S023800 | Open fracture of mandible, body, other and unspecified |
| S023x00 | Open fracture of mandible, multiple sites |
| S023z00 | Fracture of mandible, open, NOS |
| S024.00 | Fracture of malar or maxillary bones, closed |
| S024.11 | Fracture of upper jaw, closed |
| S024000 | Closed fracture maxilla |
| S024100 | Closed fracture zygoma |
| S024z00 | Fracture of malar or maxillary bones, closed, NOS |
| S025.00 | Fracture of malar or maxillary bones, open |
| S025.11 | Fracture of upper jaw, open |
| S025000 | Open fracture maxilla |
| S025100 | Open fracture zygoma |
| S025z00 | Fracture of malar or maxillary bones, open, NOS |
| S026.00 | Closed orbital blow-out fracture |
| S027.00 | Open orbital blow-out fracture |
| S028.00 | Fracture of skull and facial bones |
| S028000 | Fracture of nasal bones |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S028100 | Fracture of orbital floor |
| S028200 | Fracture of malar and maxillary bones |
| S028300 | Fracture of mandible |
| S02A.00 | Le Fort I fracture maxilla |
| S02B.00 | Le Fort II fracture maxilla |
| S02C.00 | Le Fort III fracture maxilla |
| S02x.00 | Closed fracture other facial bone |
| S02x000 | Fracture of alveolus, closed |
| S02x100 | Fracture of orbit NOS, closed |
| S02x200 | Fracture of palate, closed |
| S02xz00 | Fracture of other facial bones, closed, NOS |
| S02y.00 | Open fracture other facial bone |
| S02y000 | Fracture of alveolus, open |
| S02y100 | Fracture of orbit NOS, open |
| S02y200 | Fracture of palate, open |
| S02yz00 | Fracture of other facial bones,open, NOS |
| S02z.00 | Fracture of facial bone NOS |
| S02z.11 | Jaw fracture NOS |
| S03..00 | Other and unqualified skull fractures |
| S030.00 | Closed fracture of skull NOS without intracranial injury |
| S030000 | Closed #skull NOS no intracranial inj, unspec state of consc |
| S030100 | Closed #skull NOS no intracranial inj, no loss of consc |
| S030200 | Closed #skull NOS no intracranial inj, <1hr loss of consc |
| S030300 | Closed #skull NOS no intracranial inj, 1-24hr loss of consc |
| S030400 | Closed #skull NOS no intracranial inj, >24hrs LOC + recovery |
| S030500 | Closed #skull NOS no intracranial inj,>24hr LOC not restored |
| S030600 | Closed #skull NOS no intracranial inj, LOC unspec duration |
| S030z00 | Closed #skull NOS no intracranial inj + concussion unspec |
| S031.00 | Closed fracture of skull NOS with intracranial injury |
| S031000 | Closed #skull NOS + intracranial inj, unspec state of consc |
| S031100 | Closed #skull NOS + intracranial inj, no loss of consc |
| S031200 | Closed #skull NOS + intracranial inj, <1hr loss of consc |
| S031300 | Closed #skull NOS + intracranial inj, 1-24hrs loss of consc |
| S031400 | Closed #skull NOS + intracranial inj, >24hrs LOC + recovery |
| S031500 | Closed #skull NOS + intracranial inj, >24hr LOC not restored |
| S031600 | Closed #skull NOS + intracranial inj, LOC unspec duration |
| S031z00 | Closed #skull NOS + intracranial inj + concussion unspec |
| S032.00 | Open #skull NOS without mention of intracranial injury |
| S032000 | Open #skull NOS no intracranial inj, unspec state of consc |
| S032100 | Open #skull NOS no intracranial inj, no loss of consc |
| S032200 | Open #skull NOS no intracranial inj, <1hr loss of consc |
| S032300 | Open #skull NOS no intracranial inj, 1-24hrs loss of consc |
| S032400 | Open #skull NOS no intracranial inj, >24hrs LOC + recovery |
| S032500 | Open #skull NOS no intracranial inj, >24hrs LOC not restored |
| S032600 | Open #skull NOS no intracranial inj, LOC unspec duration |
| S032z00 | Open #skull NOS no intracranial inj + concussion unspec |
| S033.00 | Open fracture of skull NOS with intracranial injury |
| S033000 | Open #skull NOS + intracranial inj, unspec state of consc |
| S033100 | Open #skull NOS + intracranial inj, no loss of consc |
| S033200 | Open #skull NOS + intracranial inj, <1hr loss of consc |
| S033300 | Open #skull NOS + intracranial inj, 1-24hrs loss of consc |
| S033400 | Open #skull NOS + intracranial inj, >24hrs LOC + recovery |
| S033500 | Open #skull NOS + intracranial inj, >24hrs LOC not restored |
| S033600 | Open #skull NOS + intracranial inj, LOC unspec duration |
| S033z00 | Open #skull NOS + intracranial inj + concussion unspec |
| S03z.00 | Skull fracture NOS |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S03z.11 | Depressed skull fracture NOS |
| S04..00 | Multiple fractures involving skull or face with other bones |
| S04..11 | Multiple face fractures |
| S04..12 | Multiple skull fractures |
| S040.00 | Mult #skull/face+other bones, closed, no intracranial injury |
| S040000 | Closed #skull/face, mult, no intracranial inj, unspec consc |
| S040100 | Closed #skull/face, mult, no intracranial inj, no loss consc |
| S040200 | Closed #skull/face, mult, no intracranial inj, <1hr LOC |
| S040300 | Closed #skull/face, mult, no intracranial inj, 1-24hrs LOC |
| S040400 | Closed #skull/face, mult,no intracran inj,>24hr LOC+recovery |
| S040500 | Closed #skull/face,mult,no intracran inj,>24hr LOC-restored |
| S040600 | Closed #skull/face,mult,no intracran inj,LOC unspec duration |
| S040z00 | Closed #skull/face,mult,no intracran inj, concussion unspec |
| S041.00 | Mult #skull/face+other bones, closed + intracranial injury |
| S041000 | Closed #skull/face, mult + intracranial inj, unspec consc |
| S041100 | Closed #skull/face, mult + intracranial inj, no loss consc |
| S041200 | Closed #skull/face, mult + intracranial inj, <1hr LOC |
| S041300 | Closed #skull/face, mult + intracranial inj, 1-24hrs LOC |
| S041400 | Closed #skull/face, mult+intracran inj, >24hr LOC+recovery |
| S041500 | Closed #skull/face, multi+intracran inj, >24hr LOC-restored |
| S041600 | Closed #skull/face,mult + intracran inj, LOC unspec duration |
| S041z00 | Closed #skull/face,mult + intracran inj, concussion unspec |
| S042.00 | Mult #skull/face + other bones, open, no intracranial injury |
| S042000 | Open #skull/face, mult, no intracranial inj, unspec consc |
| S042100 | Open #skull/face, mult, no intracranial inj, no loss consc |
| S042200 | Open #skull/face, mult, no intracranial inj, <1hr LOC |
| S042300 | Open #skull/face, mult, no intracranial inj, 1-24hrs LOC |
| S042400 | Open #skull/face, mult, no intracran inj, >24hr LOC+recovery |
| S042500 | Open #skull/face,mult,no intracran inj,>24hr LOC no restored |
| S042600 | Open #skull/face,mult,no intracran inj, LOC unspec duration |
| S042z00 | Open #skull/face,mult,no intracran inj, concussion unspec |
| S043.00 | Mult #skull/face + other bones, open + intracranial injury |
| S043000 | Open #skull/face, mult + intracranial inj, unspec consc |
| S043100 | Open #skull/face, mult + intracranial inj, no loss consc |
| S043200 | Open #skull/face, mult + intracranial inj, <1hr LOC |
| S043300 | Open #skull/face, mult + intracranial inj, 1-24hrs LOC |
| S043400 | Open #skull/face, mult + intracran inj, >24hr LOC + recovery |
| S043500 | Open #skull/face,mult + intracran inj, >24hr LOC no restored |
| S043600 | Open #skull/face, mult + intracran inj, LOC unspec duration |
| S043z00 | Open #skull/face, mult + intracran inj + concussion, unspec |
| S044.00 | Multiple fractures involving skull and facial bones |
| S04z.00 | Multiple fractures involving skull/face with other bones NOS |
| S0z..00 | Fracture of skull NOS |
| S1…00 | Fracture of neck and trunk |
| S10..00 | Fracture of spine without mention of spinal cord injury |
| S10..11 | Fracture of transverse process spine – no spinal cord lesion |
| S10..12 | Fracture of vertebra without spinal cord lesion |
| S100.00 | Closed fracture of cervical spine |
| S100.11 | Closed fracture of atlas without spinal cord lesion |
| S100.12 | Closed fracture of axis without spinal cord lesion |
| S100000 | Closed fracture of unspecified cervical vertebra |
| S100100 | Closed fracture atlas |
| S100111 | C1 vertebra closed fracture – no spinal cord lesion |
| S100200 | Closed fracture axis |
| S100211 | C2 vertebra closed fracture without spinal cord lesion |
| S100300 | Closed fracture of third cervical vertebra |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S100311 | C3 vertebra closed fracture without spinal cord lesion |
| S100400 | Closed fracture of fourth cervical vertebra |
| S100411 | C4 vertebra closed fracture without spinal cord lesion |
| S100500 | Closed fracture of fifth cervical vertebra |
| S100511 | C5 vertebra closed fracture without spinal cord lesion |
| S100600 | Closed fracture of sixth cervical vertebra |
| S100611 | C6 vertebra closed fracture without spinal cord lesion |
| S100700 | Closed fracture of seventh cervical vertebra |
| S100711 | C7 vertebra closed fracture without spinal cord lesion |
| S100800 | Closed fracture atlas, isolated arch or articular process |
| S100900 | Closed fracture atlas, comminuted |
| S100A00 | Closed fracture axis, odontoid process |
| S100B00 | Closed fracture axis, spondylolysis |
| S100C00 | Closed fracture axis, spinous process |
| S100D00 | Closed fracture axis, transverse process |
| S100E00 | Closed fracture axis, posterior arch |
| S100F00 | Closed fracture axis, tricolumnar |
| S100G00 | Closed fracture cervical vertebra, burst |
| S100H00 | Closed fracture cervical vertebra, wedge |
| S100J00 | Closed fracture cervical vertebra, spondylolysis |
| S100K00 | Closed fracture cervical vertebra, spinous process |
| S100L00 | Closed fracture cervical vertebra, transverse process |
| S100M00 | Closed fracture cervical vertebra, posterior arch |
| S100N00 | Closed fracture cervical vertebra, tricolumnar |
| S100x00 | Multiple closed fractures of cervical vertebrae |
| S100z00 | Closed fracture of cervical spine not otherwise specified |
| S101.00 | Open fracture of cervical spine |
| S101.11 | Open fracture of atlas without spinal cord lesion |
| S101.12 | Open fracture of axis without spinal cord lesion |
| S101000 | Open fracture of unspecified cervical vertebra |
| S101100 | Open fracture atlas |
| S101111 | C1 vertebra open fracture without spinal cord lesion |
| S101200 | Open fracture axis |
| S101211 | C2 vertebra open fracture without spinal cord lesion |
| S101300 | Open fracture of third cervical vertebra |
| S101311 | C3 vertebra open fracture without spinal cord lesion |
| S101400 | Open fracture of fourth cervical vertebra |
| S101411 | C4 vertebra open fracture without spinal cord lesion |
| S101500 | Open fracture of fifth cervical vertebra |
| S101511 | C5 vertebra open fracture without spinal cord lesion |
| S101600 | Open fracture of sixth cervical vertebra |
| S101611 | C6 vertebra open fracture without spinal cord lesion |
| S101700 | Open fracture of seventh cervical vertebra |
| S101711 | C7 vertebra open fracture without spinal cord lesion |
| S101800 | Open fracture atlas, isolated arch or articular process |
| S101900 | Open fracture atlas, comminuted |
| S101A00 | Open fracture axis, odontoid process |
| S101B00 | Open fracture axis, spondylolysis |
| S101C00 | Open fracture axis, spinous process |
| S101D00 | Open fracture axis, transverse process |
| S101E00 | Open fracture axis, posterior arch |
| S101F00 | Open fracture axis, tricolumnar |
| S101G00 | Open fracture cervical vertebra, burst |
| S101H00 | Open fracture cervical vertebra, wedge |
| S101J00 | Open fracture cervical vertebra, spondylolysis |
| S101K00 | Open fracture cervical vertebra, spinous process |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S101L00 | Open fracture cervical vertebra, transverse process |
| S101M00 | Open fracture cervical vertebra, posterior arch |
| S101N00 | Open fracture cervical vertebra, tricolumnar |
| S101x00 | Multiple open fractures of cervical vertebrae |
| S101z00 | Open fracture of cervical spine not otherwise specified |
| S102.00 | Closed fracture thoracic vertebra |
| S102000 | Closed fracture thoracic vertebra, burst |
| S102100 | Closed fracture thoracic vertebra, wedge |
| S102200 | Closed fracture thoracic vertebra, spondylolysis |
| S102300 | Closed fracture thoracic vertebra, spinous process |
| S102400 | Closed fracture thoracic vertebra, transverse process |
| S102500 | Closed fracture thoracic vertebra, posterior arch |
| S102600 | Closed fracture thoracic vertebra, tricolumnar |
| S102y00 | Other specified closed fracture thoracic vertebra |
| S102z00 | Closed fracture thoracic vertebra not otherwise specified |
| S103.00 | Open fracture thoracic vertebra |
| S103000 | Open fracture thoracic vertebra, burst |
| S103100 | Open fracture thoracic vertebra, wedge |
| S103200 | Open fracture thoracic vertebra, spondylolysis |
| S103300 | Open fracture thoracic vertebra, spinous process |
| S103400 | Open fracture thoracic vertebra, transverse process |
| S103500 | Open fracture thoracic vertebra, posterior arch |
| S103600 | Open fracture thoracic vertebra, tricolumnar |
| S104.00 | Closed fracture lumbar vertebra |
| S104000 | Closed fracture lumbar vertebra, burst |
| S104100 | Closed fracture lumbar vertebra, wedge |
| S104200 | Closed fracture lumbar vertebra, spondylolysis |
| S104300 | Closed fracture lumbar vertebra, spinous process |
| S104400 | Closed fracture lumbar vertebra, transverse process |
| S104500 | Closed fracture lumbar vertebra, posterior arch |
| S104600 | Closed fracture lumbar vertebra, tricolumnar |
| S105.00 | Open fracture lumbar vertebra |
| S105000 | Open fracture lumbar vertebra, burst |
| S105100 | Open fracture lumbar vertebra, wedge |
| S105200 | Open fracture lumbar vertebra, spondylolysis |
| S105300 | Open fracture lumbar vertebra, spinous process |
| S105400 | Open fracture lumbar vertebra, transverse process |
| S105500 | Open fracture lumbar vertebra, posterior arch |
| S105600 | Open fracture lumbar vertebra, tricolumnar |
| S106.00 | Closed fracture sacrum |
| S106000 | Closed compression fracture sacrum |
| S106100 | Closed vertical fracture of sacrum |
| S107.00 | Open fracture sacrum |
| S107000 | Open compression fracture sacrum |
| S107100 | Open vertical fracture of sacrum |
| S108.00 | Closed fracture pelvis, coccyx |
| S109.00 | Open fracture pelvis, coccyx |
| S10A.00 | Fracture of neck |
| S10A000 | Fracture of first cervical vertebra |
| S10A100 | Fracture of second cervical vertebra |
| S10A200 | Multiple fractures of cervical spine |
| S10B.00 | Fracture of lumbar spine and pelvis |
| S10B000 | Fracture of lumbar vertebra |
| S10B100 | Fracture of sacrum |
| S10B200 | Fracture of coccyx |
| S10B300 | Fracture of ilium |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S10B400 | Fracture of acetabulum |
| S10B500 | Fracture of pubis |
| S10B600 | Multiple fractures of lumbar spine and pelvis |
| S10x.00 | Closed fracture of spine, unspecified, |
| S10y.00 | Open fracture of spine, unspecified, |
| S10z.00 | Fracture of spine without mention of spinal cord lesion NOS |
| S11..00 | Fracture of spine with spinal cord lesion |
| S11..11 | Fracture of transverse process of spine + spinal cord lesion |
| S11..12 | Fracture of vertebra with spinal cord lesion |
| S110.00 | Closed fracture of cervical spine with cord lesion |
| S110000 | Cls spinal fracture with unspec cervical cord lesion, C1-4 |
| S110100 | Cls spinal fracture with complete cervcl cord lesion, C1-4 |
| S110200 | Cls spinal fracture with anterior cervcl cord lesion, C1-4 |
| S110300 | Cls spinal fracture with central cervical cord lesion, C1-4 |
| S110400 | Cls spinal fracture with posterior cervcl cord lesion, C1-4 |
| S110500 | Cls spinal # with incomplete cervical cord lesion, C1-4 NOS |
| S110600 | Cls spinal fracture with unspec cervical cord lesion, C5-7 |
| S110700 | Cls spinal fracture with complete cervcl cord lesion, C5-7 |
| S110800 | Cls spinal fracture with anterior cervcl cord lesion, C5-7 |
| S110900 | Cls spinal fracture with central cervical cord lesion, C5-7 |
| S110A00 | Cls spinal fracture with posterior cervcl cord lesion, C5-7 |
| S110B00 | Cls spinal # with incomplete cervical cord lesion, C5-7 NOS |
| S110z00 | Closed fracture of cervical spine with cord lesion NOS |
| S111.00 | Open fracture of cervical spine with spinal cord lesion |
| S111000 | Opn spinal fracture with unspec cervical cord lesion, C1-4 |
| S111100 | Opn spinal fracture with complete cervcl cord lesion, C1-4 |
| S111200 | Opn spinal fracture with anterior cervcl cord lesion, C1-4 |
| S111300 | Open spinal fracture with central cervical cord lesion, C1-4 |
| S111400 | Opn spinal fracture with posterior cervcl cord lesion, C1-4 |
| S111500 | Opn spinal # with incomplete cervical cord lesion, C1-4 NOS |
| S111600 | Opn spinal fracture with unspec cervical cord lesion, C5-7 |
| S111700 | Opn spinal fracture with complete cervcl cord lesion, C5-7 |
| S111800 | Opn spinal fracture with anterior cervcl cord lesion, C5-7 |
| S111900 | Open spinal fracture with central cervical cord lesion, C5-7 |
| S111A00 | Opn spinal fracture with posterior cervcl cord lesion, C5-7 |
| S111B00 | Opn spinal # with incomplete cervical cord lesion, C5-7 NOS |
| S111z00 | Open fracture of cervical spine with spinal cord lesion NOS |
| S112.00 | Closed fracture of thoracic spine with spinal cord lesion |
| S112000 | Cls spinal fracture with unspec thoracic cord lesion,T1-6 |
| S112100 | Cls spinal fracture wth complete thoracic cord lesion,T1-6 |
| S112200 | Cls spinal fracture wth anterior thoracic cord lesion,T1-6 |
| S112300 | Cls spinal fracture with central thoracic cord lesion, T1-6 |
| S112400 | Cls spinal fracture with posterior thorac cord lesion, T1-6 |
| S112500 | Cls spinal # with incomplete thoracic cord lesion, T1-6 NOS |
| S112600 | Cls spinal fracture with unspec thoracic cord lesion, T7-12 |
| S112700 | Cls spinal fracture with complete thorac cord lesion, T7-12 |
| S112800 | Cls spinal fracture with anterior thorac cord lesion, T7-12 |
| S112900 | Cls spinal fracture with central thoracid cord lesion, T7-12 |
| S112A00 | Cls spinal fracture with posterior thorac cord lesion, T7-12 |
| S112B00 | Cls spinal # with incomplete thoracid cord lesion, T7-12 NOS |
| S112z00 | Closed fracture of thoracic spine with cord lesion NOS |
| S113.00 | Open fracture of thoracic spine with spinal cord lesion |
| S113000 | Opn spinal fracture with unspec thoracic cord lesion, T1-6 |
| S113100 | Opn spinal fracture with complete thorac cord lesion, T1-6 |
| S113200 | Opn spinal fracture with anterior thorac cord lesion, T1-6 |
| S113300 | Open spinal fracture with central thoracic cord lesion, T1-6 |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S113400 | Opn spinal fracture with posterior thorac cord lesion, T1-6 |
| S113500 | Opn spinal # with incomplete thoracic cord lesion, T1-6 NOS |
| S113600 | Opn spinal fracture with unspec thoracic cord lesion, T7-12 |
| S113700 | Opn spinal fracture with complete thorac cord lesion, T7-12 |
| S113800 | Opn spinal fracture with anterior thorac cord lesion, T7-12 |
| S113900 | Op spinal fracture with central thoracic cord lesion, T7-12 |
| S113A00 | Opn spinal fracture with posterior thorac cord lesion, T7-12 |
| S113B00 | Opn spinal # with incomplete thoracic cord lesion, T7-12 NOS |
| S113z00 | Open fracture of thoracic spine with spinal cord lesion NOS |
| S114.00 | Closed fracture of lumbar spine with spinal cord lesion |
| S114000 | Closed spinal fracture with unspecified lumbar cord lesion |
| S114100 | Closed spinal fracture with complete lumbar cord lesion |
| S114200 | Closed spinal fracture with anterior lumbar cord lesion |
| S114300 | Closed spinal fracture with central lumbar cord lesion |
| S114400 | Closed spinal fracture with posterior lumbar cord lesion |
| S114500 | Closed spinal fracture with cauda 382quine lesion |
| S115.00 | Open fracture of lumbar spine with spinal cord lesion |
| S115000 | Open spinal fracture with unspecified lumbar cord lesion |
| S115100 | Open spinal fracture with complete lumbar cord lesion |
| S115200 | Open spinal fracture with anterior lumbar cord lesion |
| S115300 | Open spinal fracture with central lumbar cord lesion |
| S115400 | Open spinal fracture with posterior lumbar cord lesion |
| S115500 | Open spinal fracture with cauda 382quine lesion |
| S115z00 | Open spinal fracture with incomplete lumbar cord lesion NOS |
| S116.00 | Closed fracture of sacrum with spinal cord lesion |
| S116000 | Closed fracture of sacrum with unspec spinal cord lesion |
| S116100 | Closed fracture of sacrum with complete cauda 382quine lesion |
| S116200 | Closed fracture of sacrum with other cauda 382quine injury |
| S116300 | Closed fracture of sacrum with other spinal cord injury |
| S116z00 | Closed fracture of sacrum with spinal cord lesion NOS |
| S117.00 | Open fracture of sacrum with spinal cord lesion |
| S117000 | Open fracture of sacrum with unspecified spinal cord lesion |
| S117100 | Open fracture of sacrum with complete cauda 382quine lesion |
| S117200 | Open fracture of sacrum with other cauda 382quine injury |
| S117300 | Open fracture of sacrum with other spinal cord injury |
| S117z00 | Open fracture of sacrum with spinal cord lesion NOS |
| S118.00 | Closed fracture of coccyx with spinal cord lesion |
| S118000 | Closed fracture of coccyx with unspec spinal cord lesion |
| S118100 | Closed fracture of coccyx with complete cauda 382quine lesion |
| S118200 | Closed fracture of coccyx with other cauda 382quine injury |
| S118300 | Closed fracture of coccyx with other spinal cord injury |
| S118z00 | Closed fracture of coccyx with spinal cord lesion NOS |
| S119.00 | Open fracture of coccyx with spinal cord lesion |
| S119000 | Open fracture of coccyx with unspecified spinal cord lesion |
| S119100 | Open fracture of coccyx with complete cauda 382quine lesion |
| S119200 | Open fracture of coccyx with other cauda 382quine injury |
| S119300 | Open fracture of coccyx with other spinal cord injury |
| S119z00 | Open fracture of coccyx with spinal cord lesion NOS |
| S11x.00 | Closed fracture of spine with spinal cord lesion unspecified |
| S11y.00 | Open fracture of spine with spinal cord lesion unspecified |
| S11z.00 | Fracture of spine with spinal cord lesion NOS |
| S12..00 | Fracture of rib(s), sternum, larynx and trachea |
| S120.00 | Closed fracture rib |
| S120000 | Closed fracture of rib, unspecified |
| S120100 | Closed fracture of one rib |
| S120200 | Closed fracture of two ribs |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S120300 | Closed fracture of three ribs |
| S120400 | Closed fracture of four ribs |
| S120500 | Closed fracture of five ribs |
| S120600 | Closed fracture of six ribs |
| S120700 | Closed fracture of seven ribs |
| S120800 | Closed fracture of eight or more ribs |
| S120900 | Closed fracture multiple ribs |
| S120A00 | Cough fracture |
| S120z00 | Closed fracture of rib(s) NOS |
| S121.00 | Open fracture rib |
| S121000 | Open fracture of rib, unspecified |
| S121100 | Open fracture of one rib |
| S121200 | Open fracture of two ribs |
| S121300 | Open fracture of three ribs |
| S121400 | Open fracture of four ribs |
| S121500 | Open fracture of five ribs |
| S121600 | Open fracture of six ribs |
| S121700 | Open fracture of seven ribs |
| S121800 | Open fracture of eight or more ribs |
| S121900 | Open fracture multiple ribs |
| S121z00 | Open fracture of rib(s) NOS |
| S122.00 | Closed fracture sternum |
| S123.00 | Open fracture sternum |
| S124.00 | Flail chest |
| S124000 | Closed flail chest |
| S124100 | Open flail chest |
| S125.00 | Closed fracture larynx and trachea |
| S125000 | Closed fracture larynx |
| S125100 | Closed fracture of hyoid bone |
| S125200 | Closed fracture of thyroid cartilage |
| S125300 | Closed fracture of trachea |
| S125z00 | Closed fracture of larynx and trachea NOS |
| S126.00 | Open fracture larynx and trachea |
| S126000 | Open fracture larynx |
| S126100 | Open fracture of hyoid bone |
| S126200 | Open fracture of thyroid cartilage |
| S126300 | Open fracture of trachea |
| S126z00 | Open fracture of larynx and trachea NOS |
| S127.00 | Fracture of rib |
| S127000 | Multiple fractures of ribs |
| S127100 | Cough fracture of ribs |
| S128.00 | Fracture of sternum |
| S12X.00 | Fracture of bony thorax, part unspecified |
| S12X000 | Closed fracture of bony thorax part unspecified |
| S12X100 | Open fracture of bony thorax part unspecified |
| S12y.00 | Fracture of other parts of bony thorax |
| S12y000 | Closed fracture of other parts of bony thorax |
| S12y100 | Open fracture of other parts of bony thorax |
| S12z.00 | Fracture of rib(s), sternum, larynx or trachea NOS |
| S12z.11 | Rib fracture NOS |
| S12z.12 | Sternum fracture NOS |
| S13..00 | Fracture or disruption of pelvis |
| S130.00 | Closed fracture acetabulum |
| S130000 | Closed fracture acetabulum, anterior lip alone |
| S130100 | Closed fracture acetabulum, posterior lip alone |
| S130200 | Closed fracture acetabulum, anterior column |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S130300 | Closed fracture acetabulum, posterior column |
| S130400 | Closed fracture acetabulum, floor |
| S130500 | Closed fracture acetabulum, double column transverse |
| S130600 | Closed fracture acetabulum, double column unspecified |
| S130y00 | Other specified closed fracture acetabulum |
| S130z00 | Closed fracture acetabulum NOS |
| S131.00 | Open fracture acetabulum |
| S131000 | Open fracture acetabulum, anterior lip alone |
| S131100 | Open fracture acetabulum, posterior lip alone |
| S131200 | Open fracture acetabulum, anterior column |
| S131300 | Open fracture acetabulum, posterior column |
| S131400 | Open fracture acetabulum, floor |
| S131500 | Open fracture acetabulum, double column transverse |
| S131600 | Open fracture acetabulum, double column unspecified |
| S131y00 | Other specified open fracture acetabulum |
| S131z00 | Open fracture acetabulum NOS |
| S132.00 | Closed fracture pubis |
| S132000 | Closed fracture pelvis, single pubic ramus |
| S132100 | Closed fracture pelvis, multiple pubic rami – stable |
| S132200 | Closed fracture pelvis, multiple pubic rami – unstable |
| S132y00 | Other specified closed fracture pubis |
| S132z00 | Closed fracture pubis NOS |
| S133.00 | Open fracture of pubis |
| S133000 | Open fracture pelvis, single pubic ramus |
| S133100 | Open fracture pelvis, multiple pubic rami – stable |
| S133200 | Open fracture pelvis, multiple pubic rami – unstable |
| S133y00 | Other specified open fracture of pubis |
| S133z00 | Open fracture of pubis NOS |
| S134.00 | Other or multiple closed fracture of pelvis |
| S134000 | Closed fracture of ilium, unspecified |
| S134100 | Closed fracture pelvis, ischium |
| S134200 | Closed multiple disruptions of pelvis |
| S134300 | Closed fracture pelvis, ischial tuberosity |
| S134400 | Closed fracture pelvis, anterior superior iliac spine |
| S134500 | Closed fracture pelvis, anterior inferior iliac spine |
| S134600 | Closed fracture pelvis, iliac wing |
| S134700 | Closed vertical fracture of ilium |
| S134800 | Closed fracture dislocation of sacro-iliac joint |
| S134z00 | Other or multiple closed fracture of pelvis NOS |
| S135.00 | Other or multiple open fracture of pelvis |
| S135000 | Open fracture of ilium, unspecified |
| S135100 | Open fracture pelvis, ischium |
| S135200 | Open multiple disruptions of pelvis |
| S135300 | Open fracture pelvis, ischial tuberosity |
| S135400 | Open fracture pelvis, anterior superior iliac spine |
| S135500 | Open fracture pelvis, anterior inferior iliac spine |
| S135600 | Open fracture pelvis, iliac wing |
| S135700 | Open vertical fracture of ilium |
| S135800 | Open fracture dislocation of sacro-iliac joint |
| S135y00 | Other open fracture of pelvis |
| S135z00 | Other/multiple open fracture of pelvis NOS |
| S136.00 | Closed complete rupture of pelvic ring |
| S136000 | Closed complete rupture pubic symphysis |
| S136100 | Closed complete rupture sacro-iliac joint |
| S137.00 | Open complete rupture of pelvic ring |
| S137000 | Open complete rupture pubic symphysis |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S137100 | Open complete rupture of sacro-iliac joint |
| S138.00 | Traumatic rupture of symphysis pubis |
| S13y.00 | Closed fracture of pelvis NOS |
| S13z.00 | Open fracture of pelvis NOS |
| S14..00 | Fracture of ill-defined bones of trunk |
| S140.00 | Closed fracture of ill-defined bone of trunk |
| S141.00 | Open fracture of ill-defined bone of trunk |
| S14z.00 | Fracture of ill-defined bone of trunk NOS |
| S15..00 | Fracture of thoracic vertebra |
| S150.00 | Multiple fractures of thoracic spine |
| S150000 | Closed multiple fractures of thoracic spine |
| S150100 | Open multiple fracture of thoracic spine |
| S1z..00 | Fracture of neck and trunk NOS |
| S2…00 | Fracture of upper limb |
| S2…11 | Arm fracture |
| S20..00 | Fracture of clavicle |
| S20..11 | Collar bone fracture |
| S200.00 | Closed fracture of clavicle |
| S200000 | Closed fracture of clavicle, unspecified part |
| S200100 | Closed fracture clavicle, medial end |
| S200200 | Closed fracture clavicle, shaft |
| S200300 | Closed fracture clavicle, lateral end |
| S200z00 | Closed fracture of clavicle NOS |
| S201.00 | Open fracture of clavicle |
| S201000 | Open fracture of clavicle, unspecified part |
| S201100 | Open fracture clavicle, medial end |
| S201200 | Open fracture clavicle, shaft |
| S201300 | Open fracture clavicle, lateral end |
| S201z00 | Open fracture of clavicle NOS |
| S20z.00 | Fracture of clavicle NOS |
| S21..00 | Fracture of scapula |
| S21..11 | Shoulder blade fracture |
| S210.00 | Closed fracture of scapula |
| S210000 | Closed fracture of scapula, unspecified part |
| S210100 | Closed fracture scapula, acromion |
| S210200 | Closed fracture scapula, coracoid |
| S210300 | Closed fracture scapula, glenoid |
| S210400 | Closed fracture scapula, blade |
| S210500 | Closed fracture scapula, spine |
| S210600 | Closed fracture scapula, neck |
| S210z00 | Closed fracture of scapula NOS |
| S211.00 | Open fracture of scapula |
| S211000 | Open fracture of scapula, unspecified part |
| S211100 | Open fracture scapula, acromion |
| S211200 | Open fracture scapula, coracoid |
| S211300 | Open fracture scapula, glenoid |
| S211400 | Open fracture scapula, blade |
| S211500 | Open fracture scapula, spine |
| S211600 | Open fracture scapula, neck |
| S211z00 | Open fracture of scapula NOS |
| S21z.00 | Fracture of scapula NOS |
| S22..00 | Fracture of humerus |
| S220.00 | Closed fracture of the proximal humerus |
| S220000 | Closed fracture of proximal humerus, unspecified part |
| S220100 | Closed fracture proximal humerus, neck |
| S220200 | Closed fracture of proximal humerus, anatomical neck |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S220300 | Closed fracture proximal humerus, greater tuberosity |
| S220400 | Closed fracture proximal humerus, head |
| S220500 | Closed fracture of humerus, upper epiphysis |
| S220600 | Closed fracture proximal humerus, three part |
| S220700 | Closed fracture proximal humerus, four part |
| S220z00 | Closed fracture of proximal humerus not otherwise specified |
| S221.00 | Open fracture of the proximal humerus |
| S221.11 | Shoulder fracture – open |
| S221000 | Open fracture of proximal humerus, unspecified part |
| S221100 | Open fracture proximal humerus, neck |
| S221200 | Open fracture of proximal humerus, anatomical neck |
| S221300 | Open fracture proximal humerus, greater tuberosity |
| S221400 | Open fracture proximal humerus, head |
| S221500 | Open fracture of humerus, upper epiphysis |
| S221600 | Open fracture proximal humerus, three part |
| S221700 | Open fracture proximal humerus, four part |
| S221z00 | Open fracture of proximal humerus not otherwise specified |
| S222.00 | Closed fracture of humerus, shaft or unspecified part |
| S222000 | Closed fracture of humerus NOS |
| S222100 | Closed fracture of humerus, shaft |
| S222z00 | Closed fracture of humerus, shaft or unspecified part NOS |
| S223.00 | Open fracture of humerus, shaft or unspecified part |
| S223000 | Open fracture of humerus NOS |
| S223100 | Open fracture of humerus, shaft |
| S223z00 | Open fracture of humerus, shaft or unspecified part NOS |
| S224.00 | Closed fracture of the distal humerus |
| S224.11 | Elbow fracture – closed |
| S224000 | Closed fracture of elbow, unspecified part |
| S224100 | Closed fracture distal humerus, supracondylar |
| S224200 | Closed fracture distal humerus, lateral condyle |
| S224300 | Closed fracture distal humerus, medial condyle |
| S224400 | Closed fracture of distal humerus, condyle(s) unspecified |
| S224500 | Closed fracture of distal humerus, trochlea |
| S224600 | Closed fracture distal humerus, lateral epicondyle |
| S224700 | Closed fracture distal humerus, medial epicondyle |
| S224800 | Closed fracture distal humerus, capitellum |
| S224900 | Closed fracture distal humerus, bicondylar (T-Y fracture) |
| S224x00 | Closed fracture of distal humerus, multiple |
| S224z00 | Closed fracture of distal humerus, not otherwise specified |
| S225.00 | Open fracture of the distal humerus |
| S225.11 | Elbow fracture – open |
| S225000 | Open fracture of elbow, unspecified part |
| S225100 | Open fracture distal humerus, supracondylar |
| S225200 | Open fracture distal humerus, lateral condyle |
| S225300 | Open fracture distal humerus, medial condyle |
| S225400 | Open fracture of distal humerus, condyle(s) unspecified |
| S225500 | Open fracture of distal humerus, trochlea |
| S225600 | Open fracture distal humerus, lateral epicondyle |
| S225700 | Open fracture distal humerus, medial epicondyle |
| S225800 | Open fracture distal humerus, capitellum |
| S225900 | Open fracture distal humerus, bicondylar (T-Y fracture) |
| S225x00 | Open fracture of distal humerus, multiple |
| S225z00 | Open fracture of distal humerus, not otherwise specified |
| S226.00 | Fracture of upper end of humerus |
| S227.00 | Fracture of shaft of humerus |
| S228.00 | Fracture of lower end of humerus |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S22z.00 | Fracture of humerus NOS |
| S23..00 | Fracture of radius and ulna |
| S23..11 | Forearm fracture |
| S230.00 | Closed fracture of proximal radius and ulna |
| S230000 | Closed fracture of proximal forearm, unspecified part |
| S230100 | Closed fracture olecranon, extra-articular |
| S230200 | Closed fracture of ulna, coronoid |
| S230300 | Closed Monteggia's fracture |
| S230400 | Closed fracture of proximal ulna, comminuted |
| S230500 | Closed fracture of the proximal ulna |
| S230600 | Closed fracture radius, head |
| S230700 | Closed fracture radius, neck |
| S230711 | Closed # radius neck |
| S230800 | Closed fracture proximal radius, comminuted |
| S230900 | Closed fracture of the proximal radius |
| S230A00 | Closed fracture radius and ulna, proximal |
| S230B00 | Closed fracture olecranon, intra-articular |
| S230z00 | Closed fracture of proximal forearm not otherwise specified |
| S231.00 | Open fracture of proximal radius and ulna |
| S231000 | Open fracture of proximal forearm, unspecified |
| S231100 | Open fracture olecranon, extra-articular |
| S231200 | Open fracture of ulna, coronoid |
| S231300 | Open Monteggia's fracture |
| S231400 | Open fracture proximal ulna, comminuted |
| S231500 | Open fracture of the proximal ulna |
| S231600 | Open fracture radial head |
| S231700 | Open fracture radial neck |
| S231800 | Open fracture proximal radius, comminuted |
| S231900 | Open fracture of the proximal radius |
| S231A00 | Open fracture radius and ulna, proximal |
| S231B00 | Open fracture olecranon, intra-articular |
| S231z00 | Open fracture of forearm, upper end, NOS |
| S232.00 | Closed fracture of radius and ulna, shaft |
| S232000 | Closed fracture of radius, shaft, unspecified |
| S232100 | Closed fracture of the radial shaft |
| S232200 | Closed fracture of the ulnar shaft |
| S232300 | Closed fracture radius and ulna, middle |
| S232z00 | Closed fracture of radius and ulna, shaft, NOS |
| S233.00 | Open fracture of radius and ulna, shaft |
| S233000 | Open fracture of radius, shaft, unspecified |
| S233100 | Open fracture of the radial shaft |
| S233200 | Open fracture of the ulnar shaft |
| S233300 | Open fracture radius and ulna, middle |
| S233z00 | Open fracture of radius and ulna, shaft, NOS |
| S234.00 | Closed fracture of radius and ulna, lower end |
| S234.11 | Wrist fracture – closed |
| S234000 | Closed fracture of forearm, lower end, unspecified |
| S234100 | Closed Colles' fracture |
| S234111 | Smith's fracture – closed |
| S234200 | Closed fracture of the distal radius, unspecified |
| S234211 | Dupuytren's fracture, radius – closed |
| S234300 | Closed fracture of ulna, styloid process |
| S234400 | Closed fracture of ulna, lower epiphysis |
| S234500 | Closed fracture distal ulna, unspecified |
| S234600 | Closed fracture radius and ulna, distal |
| S234700 | Closed Smith's fracture |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S234800 | Closed Galeazzi fracture |
| S234900 | Closed volar Barton's fracture |
| S234911 | Closed volar Barton's fracture-dislocation |
| S234912 | Closed volar Barton fracture-subluxation |
| S234A00 | Closd dorsal Barton's fracture |
| S234A11 | Closed dorsal Barton's fracture-dislocation |
| S234A12 | Closed dorsal Barton fracture-subluxation |
| S234B00 | Closed fracture radial styloid |
| S234C00 | Closed fracture distal radius, intra-articular, die-punch |
| S234D00 | Closed fracture distal radius, extra-articular, other type |
| S234E00 | Closed fracture distal radius, intra-articular, other type |
| S234F00 | Closed Barton's fracture |
| S234G00 | Greenstick fracture of distal radius |
| S234z00 | Closed fracture of forearm, lower end, NOS |
| S235.00 | Open fracture of radius and ulna, lower end |
| S235.11 | Wrist fracture – open |
| S235000 | Open fracture of forearm, lower end, unspecified |
| S235100 | Open Colles' fracture |
| S235111 | Smith's fracture – open |
| S235200 | Open fracture of the distal radius, unspecified |
| S235211 | Dupuytren's fracture, radius – open |
| S235300 | Open fracture of ulna, styloid process |
| S235400 | Open fracture of ulna, lower epiphysis |
| S235500 | Open fracture distal ulna – other |
| S235600 | Open fracture radius and ulna, distal |
| S235700 | Open Smith's fracture |
| S235800 | Open Galeazzi fracture |
| S235900 | Open volar Barton's fracture |
| S235911 | Open volar Barton fracture-dislocation |
| S235912 | Open volar Barton fracture-subluxation |
| S235A00 | Open dorsal Barton's fracture |
| S235A11 | Open dorsal Barton's fracture-dislocation |
| S235A12 | Open dorsal Barton's fracture-subluxation |
| S235B00 | Open fracture radial styloid |
| S235C00 | Open fracture distal radius, intra-articular, die-punch |
| S235D00 | Open fracture distal radius, extra-articular other type |
| S235E00 | Open fracture distal radius, intra-articular other type |
| S235F00 | Open Barton's fracture |
| S235z00 | Open fracture of forearm, lower end, NOS |
| S236.00 | Fracture of upper end of ulna |
| S237.00 | Fracture of upper end of radius |
| S238.00 | Fracture of shaft of ulna |
| S239.00 | Fracture of shaft of radius |
| S23A.00 | Fracture of shafts of both ulna and radius |
| S23B.00 | Fracture of lower end of radius |
| S23C.00 | Fracture of lower end of both ulna and radius |
| S23x.00 | Closed fracture of radius and ulna, unspecified part |
| S23x000 | Closed fracture of forearm, unspecified |
| S23x100 | Closed fracture of radius (alone), unspecified |
| S23x111 | Fracture of radius NOS |
| S23x200 | Closed fracture of ulna (alone), unspecified |
| S23x211 | Fracture of ulna NOS |
| S23x300 | Closed fracture of the radius and ulna |
| S23xz00 | Closed fracture of radius and ulna, NOS |
| S23y.00 | Open fracture of radius and ulna, unspecified part |
| S23y000 | Open fracture of forearm, unspecified |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S23y100 | Open fracture of radius (alone), unspecified |
| S23y200 | Open fracture of ulna (alone), unspecified |
| S23y300 | Open fracture of the radius and ulna |
| S23yz00 | Open fracture of radius and ulna, NOS |
| S23z.00 | Fracture of radius and ulna, NOS |
| S24..00 | Fracture of carpal bone |
| S24..11 | Hand fracture – carpal bone |
| S240.00 | Closed fracture of carpal bone |
| S240000 | Closed fracture of carpal bone, unspecified |
| S240100 | Closed fracture of the scaphoid |
| S240200 | Closed fracture lunate |
| S240300 | Closed fracture triquetral |
| S240400 | Closed fracture pisiform |
| S240500 | Closed fracture trapezium |
| S240600 | Closed fracture trapezoid |
| S240700 | Closed fracture capitate |
| S240800 | Closed fracture hamate |
| S240900 | Closed fracture hamate, hook |
| S240A00 | Closed fracture scaphoid, proximal pole |
| S240B00 | Closed fracture scaphoid, waist, transverse |
| S240C00 | Closed fracture scaphoid, waist, oblique |
| S240D00 | Closed fracture scaphoid, waist, comminuted |
| S240E00 | Closed fracture scaphoid, tuberosity |
| S240F00 | Closed fracture carpal bones, multiple |
| S240y00 | Closed fracture of other carpal bone |
| S240z00 | Closed fracture of carpal bone NOS |
| S241.00 | Open fracture of carpal bone |
| S241000 | Open fracture of carpal bone, unspecified |
| S241100 | Open fracture of the scaphoid |
| S241200 | Open fracture lunate |
| S241300 | Open fracture triquetral |
| S241400 | Open fracture pisiform |
| S241500 | Open fracture trapezium |
| S241600 | Open fracture trapezoid |
| S241700 | Open fracture capitate |
| S241800 | Open fracture hamate |
| S241900 | Open fracture hamate, hook |
| S241A00 | Open fracture scaphoid, proximal pole |
| S241B00 | Open fracture scaphoid, waist, transverse |
| S241C00 | Open fracture scaphoid, waist, oblique |
| S241D00 | Open fracture scaphoid, waist, comminuted |
| S241E00 | Open fracture scaphoid, tuberosity |
| S241F00 | Open fracture carpal bones, multiple |
| S241y00 | Open fracture of other carpal bone |
| S241z00 | Open fracture of carpal bone NOS |
| S242.00 | Fracture at wrist and hand level |
| S242000 | Fracture of scaphoid |
| S242100 | Fracture of first metacarpal bone |
| S242200 | Fracture of other metacarpal bone |
| S242300 | Multiple fractures of metacarpal bones |
| S24z.00 | Fracture of carpal bone NOS |
| S25..00 | Fracture of metacarpal bone |
| S25..11 | Hand fracture – metacarpal bone |
| S250.00 | Closed fracture of metacarpal bone(s) |
| S250000 | Closed fracture of metacarpal bone (s), site unspecified |
| S250100 | Cls # thumb metacarpal base, intra-articular, Bennett |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S250200 | Closed fracture finger metacarpal base |
| S250300 | Closed fracture finger metacarpal shaft |
| S250400 | Closed fracture finger metacarpal neck |
| S250500 | Closed fracture finger metacarpal head |
| S250600 | Closed fracture finger metacarpal |
| S250700 | Closed fracture finger metacarpal, multiple |
| S250800 | Closed fracture of thumb metacarpal |
| S250900 | Cls # thumb metacarpal base, intra-articular, Rolando |
| S250A00 | Closed fracture thumb metacarpal shaft |
| S250B00 | Closed fracture thumb metacarpal neck |
| S250C00 | Closed fracture thumb metacarpal head |
| S250x00 | Closed fractures of multiple sites of unspecified metacarpus |
| S250z00 | Closed fracture of metacarpal bone(s) NOS |
| S251.00 | Open fracture of metacarpal bone(s) |
| S251000 | Open fracture of metacarpal bone(s), site unspecified |
| S251100 | Opn # thumb metacarpal base, intra-articular, Bennett |
| S251200 | Open fracture finger metacarpal base |
| S251300 | Open fracture finger metacarpal shaft |
| S251400 | Open fracture finger metacarpal neck |
| S251500 | Open fracture finger metacarpal head |
| S251600 | Open fracture finger metacarpal |
| S251700 | Open fracture finger metacarpal, multiple |
| S251800 | Open fracture of thumb metacarpal |
| S251900 | Opn # thumb metacarpal base, intra-articular, Rolando |
| S251A00 | Open fracture thumb metacarpal shaft |
| S251B00 | Open fracture thumb metacarpal neck |
| S251C00 | Open fracture thumb metacarpal head |
| S251x00 | Open fractures of multiple sites of unspecified metacarpus |
| S251z00 | Open fracture of metacarpal bone(s) NOS |
| S252.00 | Closed fracture sesamoid bone of hand |
| S253.00 | Open fracture sesamoid bone of hand |
| S26..00 | Fracture of one or more phalanges of hand |
| S26..11 | Finger fracture |
| S26..12 | Thumb fracture excluding base |
| S260.00 | Closed fracture of one or more phalanges of hand |
| S260000 | Closed fracture of phalanx or phalanges, unspecified |
| S260100 | Clsd # mid/prox phalanx/phalanges, unspecified part |
| S260200 | Cls # distal phalanx or phalanges, unspecified part |
| S260300 | Closed fracture thumb proximal phalanx |
| S260400 | Closed fracture thumb proximal phalanx, base |
| S260500 | Closed fracture thumb proximal phalanx, shaft |
| S260600 | Closed fracture thumb proximal phalanx, neck |
| S260700 | Closed fracture thumb proximal phalanx, head |
| S260800 | Closed fracture thumb distal phalanx |
| S260900 | Closed fracture thumb distal phalanx, base |
| S260A00 | Closed fracture thumb distal phalanx, shaft |
| S260B00 | Closed fracture thumb distal phalanx, tuft |
| S260C00 | Closed fracture thumb distal phalanx, mallet |
| S260D00 | Closed fracture finger proximal phalanx |
| S260E00 | Closed fracture finger proximal phalanx, base |
| S260F00 | Closed fracture finger proximal phalanx, shaft |
| S260G00 | Closed fracture finger proximal phalanx, neck |
| S260H00 | Closed fracture finger proximal phalanx, head |
| S260J00 | Closed fracture finger proximal phalanx, multiple |
| S260K00 | Closed fracture finger middle phalanx |
| S260L00 | Closed fracture finger middle phalanx, base |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S260M00 | Closed fracture finger middle phalanx, shaft |
| S260N00 | Closed fracture finger middle phalanx, neck |
| S260P00 | Closed fracture finger middle phalanx, head |
| S260Q00 | Closed fracture finger middle phalanx, multiple |
| S260R00 | Closed fracture finger distal phalanx |
| S260S00 | Closed fracture finger distal phalanx, base |
| S260T00 | Closed fracture finger distal phalanx, shaft |
| S260U00 | Closed fracture finger distal phalanx, tuft |
| S260V00 | Closed fracture finger distal phalanx, mallet |
| S260W00 | Closed fracture finger distal phalanx, multiple |
| S260x00 | Closed fractures of phalanx or phalanges, multiple sites |
| S260z00 | Closed fracture of one or more phalanges of hand NOS |
| S261.00 | Open fracture of one or more phalanges of hand |
| S261000 | Open fracture of phalanx or phalanges, unspecified |
| S261100 | Opn # mid/prox phalanx or phalanges, unspecified part |
| S261200 | Opn # distal phalanx or phalanges, unspecified part |
| S261300 | Open fracture thumb proximal phalanx |
| S261400 | Open fracture thumb proximal phalanx, base |
| S261500 | Open fracture thumb proximal phalanx, shaft |
| S261600 | Open fracture thumb proximal phalanx, neck |
| S261700 | Open fracture thumb proximal phalanx, head |
| S261800 | Open fracture thumb distal phalanx |
| S261900 | Open fracture thumb distal phalanx, base |
| S261A00 | Open fracture thumb distal phalanx, shaft |
| S261B00 | Open fracture thumb distal phalanx, tuft |
| S261C00 | Open fracture thumb distal phalanx, mallet |
| S261D00 | Open fracture finger proximal phalanx |
| S261E00 | Open fracture finger proximal phalanx, base |
| S261F00 | Open fracture finger proximal phalanx, shaft |
| S261G00 | Open fracture finger proximal phalanx, neck |
| S261H00 | Open fracture finger proximal phalanx, head |
| S261J00 | Open fracture finger proximal phalanx, multiple |
| S261K00 | Open fracture finger middle phalanx |
| S261L00 | Open fracture finger middle phalanx, base |
| S261M00 | Open fracture finger middle phalanx, shaft |
| S261N00 | Open fracture finger middle phalanx, neck |
| S261P00 | Open fracture finger middle phalanx, head |
| S261Q00 | Open fracture finger middle phalanx, multiple |
| S261R00 | Open fracture finger distal phalanx |
| S261S00 | Open fracture finger distal phalanx, base |
| S261T00 | Open fracture finger distal phalanx, shaft |
| S261U00 | Open fracture finger distal phalanx, tuft |
| S261V00 | Open fracture finger distal phalanx, mallet |
| S261W00 | Open fracture finger distal phalanx, multiple |
| S261x00 | Open fracture of phalanx or phalanges, multiple sites |
| S261z00 | Open fracture of one or more phalanges of hand NOS |
| S262.00 | Fracture of thumb |
| S263.00 | Fracture of other finger |
| S264.00 | Multiple fractures of fingers |
| S26z.00 | Fracture of one or more phalanges of hand NOS |
| S27..00 | Multiple fractures of hand bones |
| S270.00 | Closed multiple fractures of hand bones |
| S271.00 | Open multiple fractures of hand bones |
| S27z.00 | Multiple fractures of hand bones NOS |
| S28..00 | Ill-defined fractures of upper limb |
| S28..11 | Ill-defined fracture of arm |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S280.00 | Closed ill-defined fractures of upper limb |
| S281.00 | Open ill-defined fractures of upper limb |
| S28z.00 | Ill-defined fractures of upper limb NOS |
| S29..00 | Multiple # both upper limbs & upper limb with rib + sternum |
| S29..11 | Multiple fractures of arm |
| S29..12 | Multiple rib fractures |
| S29..13 | Multiple fractures of sternum |
| S290.00 | Closed multiple #upper limbs & upper limb with rib + sternum |
| S291.00 | Open multiple #upper limbs & upper limb with rib + sternum |
| S292.00 | Multiple fractures of clavicle, scapula and humerus |
| S292000 | Closed multiple fractures of clavicle, scapula and humerus |
| S292100 | Open multiple fractures of clavicle, scapula and humerus |
| S293.00 | Multiple fractures of forearm |
| S294.00 | Fractures involving multiple regions of both upper limbs |
| S294000 | Cl fractures involving multiple regions of both upper limbs |
| S294100 | Op fractures involving multiple regions of both upper limbs |
| S29z.00 | Multiple #upper limbs & upper limb with rib + sternum NOS |
| S2A..00 | Fracture of upper limb, level unspecified |
| S2B..00 | Fracture of bone of hand |
| S2z..00 | Fracture of upper limb NOS |
| S3...00 | Fracture of lower limb |
| S3...11 | Leg fracture |
| S30..00 | Fracture of neck of femur |
| S30..11 | Hip fracture |
| S300.00 | Closed fracture proximal femur, transcervical |
| S300000 | Cls # prox femur, intracapsular section, unspecified |
| S300100 | Closed fracture proximal femur, transepiphyseal |
| S300200 | Closed fracture proximal femur, midcervical section |
| S300300 | Closed fracture proximal femur, basicervical |
| S300311 | Closed fracture, base of neck of femur |
| S300400 | Closed fracture head of femur |
| S300500 | Cls # prox femur, subcapital, Garden grade unspec. |
| S300600 | Closed fracture proximal femur, subcapital, Garden grade I |
| S300700 | Closed fracture proximal femur, subcapital, Garden grade II |
| S300800 | Closed fracture proximal femur, subcapital, Garden grade III |
| S300900 | Closed fracture proximal femur, subcapital, Garden grade IV |
| S300A00 | Closed fracture of femur, upper epiphysis |
| S300y00 | Closed fracture proximal femur, other transcervical |
| S300y11 | Closed fracture of femur, subcapital |
| S300z00 | Closed fracture proximal femur, transcervical, NOS |
| S301.00 | Open fracture proximal femur, transcervical |
| S301000 | Opn # proximal femur, intracapsular section, unspecified |
| S301100 | Open fracture proximal femur, transepiphyseal |
| S301200 | Open fracture proximal femur, midcervical section |
| S301300 | Open fracture proximal femur, basicervical |
| S301311 | Open fracture base of neck of femur |
| S301400 | Open fracture head, femur |
| S301500 | Open fracture proximal femur,subcapital, Garden grade unspec |
| S301600 | Open fracture proximal femur,subcapital, Garden grade I |
| S301700 | Open fracture proximal femur,subcapital, Garden grade II |
| S301800 | Open fracture proximal femur,subcapital, Garden grade III |
| S301900 | Open fracture proximal femur,subcapital, Garden grade IV |
| S301A00 | Open fracture of femur, upper epiphysis |
| S301y00 | Open fracture proximal femur, other transcervical |
| S301y11 | Open fracture of femur, subcapital |
| S301z00 | Open fracture proximal femur, transcervical, NOS |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S302.00 | Closed fracture of proximal femur, pertrochanteric |
| S302000 | Cls # proximal femur, trochanteric section, unspecified |
| S302011 | Closed fracture of femur, greater trochanter |
| S302012 | Closed fracture of femur, lesser trochanter |
| S302100 | Closed fracture proximal femur, intertrochanteric, two part |
| S302200 | Closed fracture proximal femur, subtrochanteric |
| S302300 | Cls # proximal femur, intertrochanteric, comminuted |
| S302400 | Closed fracture of femur, intertrochanteric |
| S302z00 | Cls # of proximal femur, pertrochanteric section, NOS |
| S303.00 | Open fracture of proximal femur, pertrochanteric |
| S303000 | Open # of proximal femur, trochanteric section, unspecified |
| S303011 | Open fracture of femur, greater trochanter |
| S303012 | Open fracture of femur, lesser trochanter |
| S303100 | Open fracture proximal femur, intertrochanteric, two part |
| S303200 | Open fracture proximal femur, subtrochanteric |
| S303300 | Open fracture proximal femur, intertrochanteric, comminuted |
| S303400 | Open fracture of femur, intertrochanteric |
| S303z00 | Open fracture of proximal femur, pertrochanteric, NOS |
| S304.00 | Pertrochanteric fracture |
| S305.00 | Subtrochanteric fracture |
| S30w.00 | Closed fracture of unspecified proximal femur |
| S30x.00 | Open fracture of unspecified proximal femur |
| S30y.00 | Closed fracture of neck of femur NOS |
| S30y.11 | Hip fracture NOS |
| S30z.00 | Open fracture of neck of femur NOS |
| S31..00 | Other fracture of femur |
| S310.00 | Closed fracture of femur, shaft or unspecified part |
| S310000 | Closed fracture of femur, unspecified part |
| S310011 | Thigh fracture NOS |
| S310012 | Upper leg fracture NOS |
| S310100 | Closed fracture shaft of femur |
| S310z00 | Closed fracture of shaft or unspecified part, NOS |
| S311.00 | Open fracture of femur, shaft or unspecified part |
| S311000 | Open fracture of femur, unspecified part |
| S311100 | Open fracture shaft of femur |
| S311z00 | Open fracture of femur, shaft or unspecified part, NOS |
| S312.00 | Closed fracture distal femur |
| S312.11 | Closed fracture of femur, distal end |
| S312000 | Closed fracture of distal femur, unspecified |
| S312100 | Closed fracture of femoral condyle, unspecified |
| S312200 | Closed fracture of femur, lower epiphysis |
| S312300 | Closed fracture distal femur, supracondylar |
| S312400 | Closed fracture distal femur, medial condyle |
| S312500 | Closed fracture distal femur, lateral condyle |
| S312600 | Closed fracture distal femur, bicondylar (T-Y fracture) |
| S312x00 | Closed fracture distal femur, comminuted/intra-articular |
| S312z00 | Closed fracture of distal femur not otherwise specified |
| S313.00 | Open fracture distal femur |
| S313.11 | Open fracture of femur, distal end |
| S313000 | Open fracture distal femur, unspecified |
| S313100 | Open fracture of femoral condyle, unspecified |
| S313200 | Open fracture of femur, lower epiphysis |
| S313300 | Open fracture distal femur, supracondylar |
| S313400 | Open fracture distal femur, medial condyle |
| S313500 | Open fracture distal femur, lateral condyle |
| S313600 | Open fracture distal femur, bicondylar (T-Y fracture) |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S313x00 | Open fracture distal femur, comminuted/intra-articular |
| S313z00 | Open fracture of distal femur not otherwise specified |
| S314.00 | Fracture of shaft of femur |
| S315.00 | Fracture of lower end of femur |
| S31z.00 | Fracture of femur, NOS |
| S32..00 | Fracture of patella |
| S32..11 | #Knee-cap |
| S320.00 | Closed fracture of the patella |
| S320000 | Closed fracture patella, transverse |
| S320100 | Closed fracture patella, proximal pole |
| S320200 | Closed fracture patella, distal pole |
| S320300 | Closed fracture patella, vertical |
| S320400 | Closed fracture patella, comminuted (stellate) |
| S321.00 | Open fracture of the patella |
| S321000 | Open fracture patella, transverse |
| S321100 | Open fracture patella, proximal pole |
| S321200 | Open fracture patella, distal pole |
| S321300 | Open fracture patella, vertical |
| S321400 | Open fracture patella, comminuted (stellate) |
| S32z.00 | Fracture of patella, NOS |
| S33..00 | Fracture of tibia and fibula |
| S330.00 | Closed fracture of tibia and fibula, proximal |
| S330000 | Closed fracture of the proximal tibia |
| S330011 | Closed fracture of tibial condyles |
| S330012 | Closed fracture of tibial tuberosity |
| S330100 | Closed fracture proximal fibula |
| S330200 | Closed fracture of tibia and fibula, proximal |
| S330300 | Closed fracture proximal tibia, medial condyle (plateau) |
| S330400 | Closed fracture proximal tibia, lateral condyle (plateau) |
| S330500 | Closed fracture proximal tibia, bicondylar |
| S330600 | Closed fracture spine, tibia |
| S330700 | Closed fracture tubercle, tibia |
| S330800 | Closed fracture fibula, head |
| S330900 | Closed fracture fibula, neck |
| S330z00 | Closed fracture of tibia and fibula, proximal NOS |
| S331.00 | Open fracture of tibia and fibula, proximal |
| S331000 | Open fracture of the proximal tibia |
| S331011 | Open fracture of tibial condyles |
| S331012 | Open fracture of tibial tuberosity |
| S331100 | Open fracture proximal fibula |
| S331200 | Open fracture of tibia and fibula, proximal |
| S331300 | Open fracture proximal tibia, medial condyle (plateau) |
| S331400 | Open fracture proximal tibia, lateral condyle (plateau) |
| S331500 | Open fracture proximal tibia, bicondylar |
| S331600 | Open fracture spine, tibia |
| S331700 | Open fracture tubercle, tibia |
| S331800 | Open fracture fibula, head |
| S331900 | Open fracture fibula, neck |
| S331A00 | Open fracture tibial plateau |
| S331z00 | Open fracture of tibia and fibula, proximal NOS |
| S332.00 | Closed fracture of tibia/fibula, shaft |
| S332000 | Closed fracture shaft of tibia |
| S332100 | Closed fracture shaft of fibula |
| S332200 | Closed fracture of tibia and fibula, shaft |
| S332z00 | Closed fracture of tibia and fibula, shaft, NOS |
| S333.00 | Open fracture of tibia/fibula, shaft |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S333000 | Open fracture shaft of tibia |
| S333100 | Open fracture shaft of fibula |
| S333200 | Open fracture of tibia and fibula, shaft |
| S333z00 | Open fracture of tibia and fibula, shaft, NOS |
| S334.00 | Closed fracture distal tibia |
| S334000 | Closed fracture distal tibia, extra-articular |
| S334100 | Closed fracture distal tibia, intra-articular |
| S335.00 | Open fracture distal tibia |
| S335000 | Open fracture distal tibia, extra-articular |
| S335100 | Open fracture distal tibia, intra-articular |
| S336.00 | Fracture of upper end of tibia |
| S336000 | Fracture tibial plateau |
| S337.00 | Fracture of shaft of tibia |
| S338.00 | Fracture of lower end of tibia |
| S339.00 | Fracture of fibula alone |
| S339000 | Closed fracture of distal fibula |
| S339100 | Open fracture of distal fibula |
| S33A.00 | Fracture of tibia |
| S33B.00 | Open fracture of distal tibia and fibula |
| S33C.00 | Closed fracture of distal tibia and fibula |
| S33x.00 | Closed fracture of tibia and fibula, unspecified part, NOS |
| S33x.11 | Lower leg fracture NOS |
| S33x000 | Closed fracture of tibia, unspecified part, NOS |
| S33x100 | Closed fracture of fibula, unspecified part, NOS |
| S33x200 | Closed fracture of tibia and fibula, unspecified part |
| S33xz00 | Closed fracture of tibia and fibula, unspecified part, NOS |
| S33y.00 | Open fracture of tibia and fibula, unspecified part, NOS |
| S33y000 | Open fracture of tibia, unspecified part, NOS |
| S33y100 | Open fracture of fibula, unspecified part, NOS |
| S33y200 | Open fracture of tibia and fibula, unspecified part |
| S33yz00 | Open fracture of tibia and fibula, unspecified part, NOS |
| S33z.00 | Fracture of tibia and fibula, NOS |
| S34..00 | Fracture of ankle |
| S340.00 | Closed fracture ankle, medial malleolus |
| S341.00 | Open fracture ankle, medial malleolus |
| S342.00 | Closed fracture ankle, lateral malleolus |
| S342000 | Closed fracture ankle, lateral malleolus, low |
| S342100 | Closed fracture ankle, lateral malleolus, high |
| S343.00 | Open fracture ankle, lateral malleolus |
| S343000 | Open fracture ankle, lateral malleolus, low |
| S343100 | Open fracture ankle, lateral malleolus, high |
| S344.00 | Closed fracture ankle, bimalleolar |
| S344.11 | Dupuytren's fracture, fibula |
| S344.12 | Pott's fracture – ankle |
| S344000 | Closed fracture ankle, bimalleolar, low fibular fracture |
| S344100 | Closed fracture ankle, bimalleolar, high fibular fracture |
| S345.00 | Open fracture ankle, bimalleolar |
| S345000 | Open fracture ankle, bimalleolar, low fibular fracture |
| S345100 | Open fracture ankle, bimalleolar, high fibular fracture |
| S346.00 | Closed fracture ankle, trimalleolar |
| S346000 | Closed fracture ankle, trimalleolar, low fibular fracture |
| S346100 | Closed fracture ankle, trimalleolar, high fibular fracture |
| S347.00 | Open fracture ankle, trimalleolar |
| S347000 | Open fracture ankle, trimalleolar, low fibular fracture |
| S347100 | Open fracture ankle, trimalleolar, high fibular fracture |
| S348.00 | Fracture of medial malleolus |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S349.00 | Fracture of lateral malleolus |
| S34x.00 | Closed fracture ankle, unspecified |
| S34y.00 | Open fracture ankle, unspecified |
| S34z.00 | Fracture of ankle, NOS |
| S35..00 | Fracture of one or more tarsal and metatarsal bones |
| S35..11 | Metatarsal bone fracture |
| S35..12 | Tarsal bone fracture |
| S350.00 | Closed fracture of calcaneus |
| S350.11 | Heel bone fracture |
| S350.12 | Os calcis fracture |
| S350000 | Closed fracture calcaneus, extra-articular |
| S350100 | Closed fracture calcaneus, intra-articular |
| S351.00 | Open fracture of calcaneus |
| S351000 | Open fractures calcaneus, extra-articular |
| S351100 | Open fractures calcaneus, intra-articular |
| S352.00 | Closed fracture of other tarsal and metatarsal bones |
| S352.11 | March fracture |
| S352000 | Closed fracture of tarsal bone, unspecified |
| S352100 | Closed fracture of talus |
| S352111 | Closed fracture of astragalus |
| S352200 | Closed fracture navicular |
| S352300 | Closed fracture cuboid |
| S352400 | Closed fracture medial cuneiform |
| S352500 | Closed fracture intermediate cuneiform |
| S352600 | Closed fracture lateral cuneiform |
| S352700 | Closed fracture metatarsal |
| S352800 | Closed fracture talus, head |
| S352900 | Closed fracture talus, neck |
| S352A00 | Closed fracture talus, body |
| S352B00 | Closed fracture metatarsal base |
| S352C00 | Closed fracture metatarsal shaft |
| S352D00 | Closed fracture metatarsal neck |
| S352E00 | Closed fracture metatarsal head |
| S352F00 | Closed fracture metatarsal, multiple |
| S352G00 | Closed tarsal fractures, multiple |
| S352H00 | Closed fracture of cuneiforms |
| S352J00 | Closed fracture of base of fifth metatarsal |
| S352z00 | Closed fracture of one or more tarsal + metatarsal bones NOS |
| S353.00 | Open fracture of other tarsal and metatarsal bones |
| S353000 | Open fracture of tarsal bone, unspecified |
| S353100 | Open fracture of talus |
| S353111 | Open fracture of astragalus |
| S353200 | Open fracture navicular |
| S353300 | Open fracture cuboid |
| S353400 | Open fracture medial cuneiform |
| S353500 | Open fracture intermediate cuneiform |
| S353600 | Open fracture lateral cuneiform |
| S353700 | Open fracture metatarsal |
| S353800 | Open fracture talus, head |
| S353900 | Open fracture talus, neck |
| S353A00 | Open fracture talus, body |
| S353B00 | Open fracture metatarsal base |
| S353C00 | Open fracture metatarsal shaft |
| S353D00 | Open fracture metatarsal neck |
| S353E00 | Open fracture metatarsal head |
| S353F00 | Open fracture metatarsal, multiple |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S353G00 | Open tarsal fractures, multiple |
| S353H00 | Open fracture cuneiforms |
| S353J00 | Open fracture of base of fifth metatarsal |
| S353z00 | Open fracture of tarsal and metatarsal bones NOS |
| S354.00 | Fracture of calcaneus |
| S355.00 | Fracture of talus |
| S356.00 | Fracture of metatarsal bone |
| S35z.00 | Fracture of tarsal and metatarsal bones NOS |
| S36..00 | Fracture of one or more phalanges of foot |
| S36..11 | Toe fracture |
| S360.00 | Closed fracture of one or more phalanges of foot |
| S360000 | Closed fracture proximal phalanx, toe |
| S360100 | Closed fracture middle phalanx, toe |
| S360200 | Closed fracture distal phalanx, toe |
| S360300 | Closed fracture multiple phalanges, toe |
| S361.00 | Open fracture of one or more phalanges of foot |
| S361000 | Open fracture proximal phalanx, toe |
| S361100 | Open fracture middle phalanx, toe |
| S361200 | Open fracture distal phalanx, toe |
| S361300 | Open fracture multiple phalanges, toe |
| S362.00 | Fracture of great toe |
| S362000 | Closed fracture of great toe |
| S362100 | Open fracture of great toe |
| S363.00 | Fracture of other toe |
| S36z.00 | Fracture of one or more phalanges of foot NOS |
| S37..00 | Fracture of lower limb, level unspecified |
| S370.00 | Closed fracture of lower limb, level unspecified |
| S371.00 | Open fracture of lower limb, level unspecified |
| S3X..00 | Fracture of lower leg, part unspecified |
| S3x..00 | Other, multiple and ill-defined fractures of lower limb |
| S3x0.00 | Other, multiple and ill-defined closed fractures lower limb |
| S3x1.00 | Other, multiple and ill-defined open fractures of lower limb |
| S3x2.00 | Multiple fractures of femur |
| S3x3.00 | Multiple fractures of lower leg |
| S3x4.00 | Multiple fractures of foot |
| S3xz.00 | Other, multiple and ill-defined fractures of lower limb NOS |
| S3y..00 | Multiple #both legs, leg + arm ,leg + rib + sternum |
| S3y0.00 | Multiple closed #both legs, leg + arm, leg + rib + sternum |
| S3y1.00 | Multiple open #both legs, leg + arm, leg + rib + sternum |
| S3yz.00 | Multiple #both legs, leg + arm, leg + rib + sternum NOS |
| S3z..00 | Fracture of unspecified bones |
| S3z..11 | Fracture NOS |
| S3z0.00 | Closed fracture of bones, unspecified |
| S3z0000 | Greenstick fracture |
| S3z1.00 | Open fracture of bones, unspecified |
| S3z2.00 | Stress fracture |
| S3zz.00 | Fracture of bones NOS |
| S4…13 | Fracture dislocations and fracture subluxations |
| S4A..00 | Fracture-dislocation or subluxation shoulder |
| S4A0.00 | Closed fracture-dislocation shoulder |
| S4A0000 | Closed fracture-dislocation shoulder joint |
| S4A0100 | Closed fracture-dislocation acromio-clavicular joint |
| S4A1.00 | Open fracture-dislocation shoulder |
| S4A1000 | Open fracture-dislocation shoulder joint |
| S4A1100 | Open fracture-dislocation acromio-clavicular joint |
| S4A2.00 | Closed fracture-subluxation shoulder |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S4A2000 | Closed fracture-subluxation shoulder joint |
| S4A2100 | Closed fracture-subluxation acromio-clavicular joint |
| S4A3.00 | Open fracture-subluxation shoulder |
| S4A3000 | Open fracture-subluxation shoulder joint |
| S4A3100 | Open fracture-subluxation acromio-clavicular joint |
| S4B..00 | Fracture-dislocation or subluxation elbow |
| S4B0.00 | Closed fracture-dislocation elbow |
| S4B0000 | Closed fracture-dislocation elbow joint |
| S4B0100 | Closed fracture-dislocation superior radio-ulnar joint |
| S4B1.00 | Open fracture-dislocation elbow |
| S4B1000 | Open fracture-dislocation elbow joint |
| S4B1100 | Open fracture-dislocation superior radio-ulnar joint |
| S4B2.00 | Closed fracture-subluxation elbow |
| S4B2000 | Closed fracture-subluxation elbow joint |
| S4B2100 | Closed fracture-subluxation superior radio-ulnar joint |
| S4B3.00 | Open fracture-subluxation elbow |
| S4B3000 | Open fracture-subluxation elbow joint |
| S4B3100 | Open fracture-subluxation superior radio-ulnar joint |
| S4C..00 | Fracture-dislocation or subluxation of wrist |
| S4C0.00 | Closed fracture dislocation of wrist |
| S4C0000 | Closed fracture-dislocation distal radio-ulnar joint |
| S4C0100 | Closed fracture-dislocation radiocarpal joint |
| S4C0200 | Closed fracture-dislocation mid carpal |
| S4C0300 | Closed fracture-dislocation, carpometacarpal joint |
| S4C0400 | Closed fracture-dislocation lunate (volar) |
| S4C0500 | Closed fracture-dislocation peri-lunate (dorsal) |
| S4C0600 | Closed fracture-dislocation peri-lunate trans-scaphoid |
| S4C0y00 | Closed fracture-dislocation other carpal |
| S4C1.00 | Open fracture dislocation wrist |
| S4C1000 | Open fracture-dislocation, distal radio-ulnar joint |
| S4C1100 | Open fracture-dislocation radiocarpal joint |
| S4C1200 | Open fracture-dislocation mid carpal |
| S4C1300 | Open fracture-dislocation carpometacarpal joint |
| S4C1400 | Open fracture-dislocation lunate (volar) |
| S4C1500 | Open fracture-dislocation peri-lunate (dorsal) |
| S4C1600 | Open fracture-dislocation peri-lunate trans-scaphoid |
| S4C1y00 | Open fracture-dislocation other carpal |
| S4C2.00 | Closed fracture-subluxation of the wrist |
| S4C2000 | Closed fracture-subluxation, distal radio-ulnar jt |
| S4C2100 | Closed fracture-subluxation radiocarpal joint |
| S4C2200 | Closed fracture-subluxation mid carpal |
| S4C2300 | Closed fracture-subluxation, carpometacarpal joint |
| S4C2400 | Closed fracture-subluxation lunate (volar) |
| S4C2500 | Closed fracture-subluxation peri-lunate (dorsal) |
| S4C2600 | Closed fracture-subluxation peri-lunate trans-scaphoid |
| S4C2y00 | Closed fracture-subluxation other carpal |
| S4C3.00 | Open fracture-subluxation of the wrist |
| S4C3000 | Open fracture-subluxation, distal radio-ulnar joint |
| S4C3100 | Open fracture-subluxation radiocarpal joint |
| S4C3200 | Open fracture-subluxation mid carpal |
| S4C3300 | Open fracture-subluxation, carpometacarpal joint |
| S4C3400 | Open fracture-subluxation lunate (volar) |
| S4C3500 | Open fracture-subluxation peri-lunate (dorsal) |
| S4C3600 | Open fracture-subluxation peri-lunate trans-scaphoid |
| S4C3y00 | Open fracture-subluxation other carpal |
| S4D..00 | Fracture-dislocation/subluxation finger/thumb |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S4D0.00 | Closed fracture-dislocation digit |
| S4D0000 | Closed fracture-dislocation digit, unspecified |
| S4D0100 | Closed fracture-dislocation, metacarpophalangeal joint |
| S4D0200 | Closed fracture-dislocation IPJ, unspecified |
| S4D0300 | Closed fracture-dislocation, distal interphalangeal joint |
| S4D0400 | Closed fracture-dislocation, proximal interphalangeal joint |
| S4D0500 | Closed fracture-dislocation, interphalangeal joint thumb |
| S4D0600 | Closed fracture-dislocation multiple digits |
| S4D1.00 | Open fracture-dislocation digit |
| S4D1000 | Open fracture-dislocation digit, unspecified |
| S4D1100 | Open fracture-dislocation, metacarpophalangeal joint |
| S4D1200 | Open fracture-dislocation IPJ, unspecified |
| S4D1300 | Open fracture-dislocation, distal interphalangeal joint |
| S4D1400 | Open fracture-dislocation, proximal interphalangeal joint |
| S4D1500 | Open fracture-dislocation, interphalangeal joint thumb |
| S4D1600 | Open fracture-dislocation multiple digits |
| S4D2.00 | Closed fracture-subluxation digit |
| S4D2000 | Closed fracture-subluxation digit, unspecified |
| S4D2100 | Closed fracture-subluxation, metacarpophalangeal joint |
| S4D2200 | Closed fracture-subluxation IPJ, unspecified |
| S4D2300 | Closed fracture-subluxation, distal interphalangeal joint |
| S4D2400 | Closed fracture-subluxation, proximal interphalangeal joint |
| S4D2500 | Closed fracture-subluxation, interphalangeal joint thumb |
| S4D2600 | Closed fracture-subluxation multiple digits |
| S4D3.00 | Open fracture-subluxation digit |
| S4D3000 | Open fracture-subluxation digit, unspecified |
| S4D3100 | Open fracture-subluxation, metacarpophalangeal joint |
| S4D3200 | Open fracture-subluxation IPJ, unspecified |
| S4D3300 | Open fracture-subluxation, distal interphalangeal joint |
| S4D3400 | Open fracture-subluxation, proximal interphalangeal joint |
| S4D3500 | Open fracture-subluxation, interphalangeal joint thumb |
| S4D3600 | Open fracture-subluxation multiple digits |
| S4E..00 | Fracture-dislocation or subluxation hip |
| S4E0.00 | Closed fracture-dislocation, hip joint |
| S4E1.00 | Open fracture-dislocation, hip joint |
| S4E2.00 | Closed fracture-subluxation, hip joint |
| S4E3.00 | Open fracture-subluxation, hip joint |
| S4F..00 | Fracture-dislocation or subluxation knee |
| S4F0.00 | Closed fracture-dislocation, knee joint |
| S4F1.00 | Open fracture-dislocation, knee joint |
| S4F2.00 | Closed fracture-subluxation, knee joint |
| S4F3.00 | Open fracture-subluxation, knee joint |
| S4F4.00 | Closed fracture-dislocation, 399atella-femoral joint |
| S4F5.00 | Open fracture-dislocation, 399atella-femoral joint |
| S4F6.00 | Closed fracture-subluxation, 399atella-femoral joint |
| S4F7.00 | Open fracture-subluxation, 399atella-femoral joint |
| S4G..00 | Fracture-dislocation or subluxation ankle |
| S4G0.00 | Closed fracture-dislocation, ankle joint |
| S4G1.00 | Open fracture-dislocation, ankle joint |
| S4G2.00 | Closed fracture-subluxation, ankle joint |
| S4G3.00 | Open fracture-subluxation, ankle joint |
| S4H..00 | Fracture-dislocation or subluxation foot |
| S4H0.00 | Closed fracture-dislocation foot |
| S4H0000 | Closed fracture-dislocation, subtalar joint |
| S4H0100 | Closed fracture-dislocation, midtarsal joint |
| S4H0200 | Closed fracture-dislocation, tarsometatarsal joint |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| S4H0400 | Closed fracture-dislocation, IPJ, single toe |
| S4H0600 | Closed fracture-dislocation, IPJ, multiple toes |
| S4H1.00 | Open fracture-dislocation, foot |
| S4H1000 | Open fracture-dislocation, subtalar joint |
| S4H1100 | Open fracture-dislocation, midtarsal joint |
| S4H1200 | Open fracture-dislocation, tarsometatarsal joint |
| S4H1300 | Open fracture-dislocation, metatarsophalangeal joint, single |
| S4H1400 | Open fracture-dislocation, IPJ, single toe |
| S4H1600 | Open fracture-dislocation, IPJ, multiple toes |
| S4H2.00 | Closed fracture-subluxation, foot |
| S4H2000 | Closed fracture-subluxation, subtalar joint |
| S4H2100 | Closed fracture-subluxation, midtarsal joint |
| S4H2200 | Closed fracture-subluxation, tarsometatarsal joint |
| S4H2400 | Closed fracture-subluxation, IPJ, single toe |
| S4H2600 | Closed fracture-subluxation, IPJ, multiple toes |
| S4H3.00 | Open fracture-subluxation, foot |
| S4H3000 | Open fracture-subluxation, subtalar joint |
| S4H3100 | Open fracture-subluxation, midtarsal joint |
| S4H3200 | Open fracture-subluxation, tarsometatarsal joint |
| S4H3300 | Open fracture-subluxation, metatarsophalangeal joint, single |
| S4H3400 | Open fracture-subluxation, IPJ, single toe |
| S4H3600 | Open fracture-subluxation, IPJ, multiple toes |
| S4J..00 | Other fracture-dislocation or subluxation |
| S4J0.00 | Other closed fracture-dislocation |
| S4J0000 | Closed fracture-dislocation of sternum |
| S4J0100 | Closed fracture-dislocation of pelvis |
| S4J1.00 | Other open fracture-dislocation |
| S4J1000 | Open fracture-dislocation of sternum |
| S4J1100 | Open fracture-dislocation of pelvis |
| S4J1200 | Open fracture-dislocation sterno-clavicular joint, anterior |
| S4J1300 | Open fracture-dislocation sterno-clavicular joint, posterior |
| S4J2.00 | Other closed fracture-subluxation |
| S4J2000 | Closed fracture-subluxation of sternum |
| S4J2100 | Closed fracture-subluxation of pelvis |
| S4J3.00 | Other open fracture-subluxation |
| S4J3000 | Open fracture-subluxation of sternum |
| S4J3100 | Open fracture-subluxation of pelvis |
| S4J3200 | Open fracture-subluxation sterno-clavicular joint, anterior |
| S4J3300 | Open fracture-subluxation sterno-clavicular joint, posterior |
| S6…00 | Intracranial injury excluding those with skull fracture |
| S6z..00 | Intracranial injury, excluding those with skull fracture NOS |
| SC00.00 | Late effect of fracture of skull and face bones |
| SC00.11 | Late effect of face fracture |
| SC00.12 | Late effect of skull fracture |
| SC01.00 | Late effect of fracture of spine/trunk without cord lesion |
| SC01000 | Late effect of fracture of cervical vertebra |
| SC01100 | Late effect of fracture of thoracic vertebra |
| SC01200 | Late effect of fracture of lumbar vertebra |
| SC02.00 | Late effect of fracture of arm |
| SC03.00 | Late effect of fracture neck of femur |
| SC04.00 | Late effect of other fracture of leg |
| SC05.00 | Late effect of multiple and unspecified fracture of bones |
| SC0X.00 | Sequelae of other fracture of thorax and pelvis |
| SC0z.11 | Delayed union of fracture |
| SC20.00 | Late effect of intracranial injury without skull fracture |
| SC3C000 | Sequelae of fracture at wrist and hand level |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| SC3D400 | Sequelae of fracture of femur |
| SD92000 | Fracture blister |
| SP04A00 | Fracture of bone autograft |
| SP04C00 | Fracture of bone allograft |
| SP22400 | Intra-operative fracture |
| SR1..00 | Fractures involving multiple body regions |
| SR10.00 | Fractures involving head with neck |
| SR10000 | Closed fractures involving head with neck |
| SR10100 | Open fractures involving head with neck |
| SR11.00 | Fractures involving thorax with lower back and pelvis |
| SR12.00 | Fractures involving multiple regions of one upper limb |
| SR12000 | Closed fractures involving multiple regions of one upp limb |
| SR12100 | Open fractures involving multiple regions of one upper limb |
| SR13.00 | Fractures involving multiple regions of one lower limb |
| SR14.00 | Fractures involving multiple regions of both lower limbs |
| SR14000 | Closd fractures involving multiple regions of both low limbs |
| SR14100 | Open fractures involving multiple regions both lower limbs |
| SR15000 | Cl fractures involving multiple regions upper with lower lmb |
| SR15100 | Open fracture 401nvolve multiple regions upper with lower lmb |
| SR16000 | Closed fracture inv thorax wth low back and pelvis and limbs |
| SR16100 | Open fracture inv thorax wth low back and pelvis and limbs |
| SR1z.00 | Multiple fractures, unspecified |
| SR1z000 | [X]Closed multiple fractures unspecified |
| SR1z100 | [X]Open multiple fractures unspecified |
| Syu0300 | [X]Fractures of other skull and facial bones |
| Syu0400 | [X]Fracture of skull and facial bones, part unspecified |
| Syu1500 | [X]Fracture of other specified cervical vertebra |
| Syu1600 | [X]Fracture of other parts of neck |
| Syu2700 | [X]Fracture of other parts of bony thorax |
| Syu2800 | [X]Fracture of bony thorax, part unspecified |
| Syu4200 | [X]Multiple fractures of clavicle, scapula and humerus |
| Syu4300 | [X]Fracture of other parts of shoulder and upper arm |
| Syu4400 | [X]Fracture of shoulder and upper arm, unspecified |
| Syu5300 | [X]Fracture of other parts of forearm |
| Syu5400 | [X]Fracture of forearm, unspecified |
| Syu6300 | [X]Fracture of other carpal bone(s) |
| Syu6400 | [X]Fracture of other metacarpal bone |
| Syu6500 | [X]Fracture of other & unspecified parts of wrist and hand |
| Syu7200 | [X]Fractures of other parts of femur |
| Syu8300 | [X]Fractures of other parts of lower leg |
| Syu8D00 | [X]Fracture of lower leg, part unspecified |
| Syu9400 | [X]Fracture of other tarsal bones |
| SyuA200 | [X]Fractures involving other combinations of body regions |
| SyuBB00 | [X]Fracture of unspecified body region |
| SyuL100 | [X]Sequelae of other fracture of thorax and pelvis |
| SyuL400 | [X]Sequelae of other fractures of lower limb |
| TC7..00 | Fracture, cause unspecified |
| Zw01.00 | [Q] Fractures involving the epiphyseal plate |
| medcode | description |
| N331.00 | Pathological fracture |
| N331.13 | Sponanteous fracture |
| N331000 | Pathological fracture of thoracic vertebra |
| N331100 | Pathological fracture of lumbar vertebra |
| N331200 | Postoophorectomy osteoporosis with pathological fracture |
| N331300 | Osteoporosis of disuse with pathological fracture |
| N331400 | Postsurgical malabsorption osteoporosis with path fracture |

**Table G.10** Continued.

| Read code | Code description |
|---|---|
| N331500 | Drug-induced osteoporosis with pathological fracture |
| N331600 | Idiopathic osteoporosis with pathological fracture |
| N331700 | Fracture of bone in neoplastic disease |
| N331800 | Osteoporosis + pathological fracture lumbar vertebrae |
| N331900 | Osteoporosis + pathological fracture thoracic vertebrae |
| N331A00 | Osteoporosis + pathological fracture cervical vertebrae |
| N331B00 | Postmenopausal osteoporosis with pathological fracture |
| N331C00 | Pathological fracture of cervical vertebra |
| N331M00 | Fragility fracture due to unspecified osteoporosis |
| N331M11 | Minimal trauma fracture due to unspecified osteoporosis |
| N331N00 | Fragility fracture |
| N331N11 | Minimal trauma fracture |
| N331y00 | Other specified pathological fracture |
| N331z00 | Pathological fracture NOS |
| Q202.00 | Fracture of clavicle due to birth trauma |
| Q203.11 | Other fractures due to birth trauma |
| Q203.12 | Other birth fracture |
| Q203000 | Fracture of humerus due to birth trauma |
| Q203100 | Fracture of radius or ulna due to birth trauma |
| Q203111 | Birth fracture of radius |
| Q203112 | Birth fracture of ulna |
| Q203200 | Fracture of femur due to birth trauma |
| Q203300 | Fracture of tibia or fibula due to birth trauma |
| Q203400 | Fracture of skull due to birth trauma |
| Q203y11 | Fracture due to birth trauma NEC |
| Q203y12 | Fracture of nose due to birth trauma |
| Q204100 | Spine fracture due to birth trauma |
| S0...00 | Fracture of skull |
| S00..00 | Fracture of vault of skull |
| S00..11 | Frontal bone fracture |
| S00..12 | Parietal bone fracture |

### *G.7.5 Identification of Read Codes Related to Failure to Thrive*

The following truncated search terms were used to identify Read codes related to failure to thrive: ‘thrive, ‘stunt’, ‘grow’, ‘weight’, ‘ftt’. Common code stems were used to identify additional relevant codes. A total of 17 relevant codes were identified. The final list of included codes is shown in Table G.11.

**Table G.11** Read codes related to failure to thrive.

| Read code | Code description |
|---|---|
| 1621.11 | Weight static |
| 1623.00 | Weight decreasing |
| 1625.00 | Abnormal weight loss |
| 1625.11 | Abnormal weight loss - symptom |
| 1627.00 | Unintentional weight loss |
| 1D1A.00 | Complaining of weight loss |
| 22A6.00 | O/E - Underweight |
| 22I2.00 | O/E - failure to thrive |
| 22I5.00 | O/E - lack of growth |
| 22IC.00 | Physical growth is cause for concern |
| R032.00 | [D]Abnormal loss of weight |
| R034100 | [D]Failure to gain weight |
| R034200 | [D]Failure to thrive |
| R034300 | [D]Lack of growth |
| R034800 | [D]Underweight |
| R034900 | [D]Non-organic failure to thrive |
| ZC2CE00 | Dietary advice for failure to thrive |

### *G.7.6 Identification of Read Codes Related to Hypocalcaemia*

The following truncated search terms were used to identify Read codes related to hypocalcaemia: ‘hypocalc’, ‘calcium’. Common code stems were used to identify additional relevant codes. A total of 7 relevant codes were identified. The final list of included codes is shown in Table G.12.

**Table G.12** Read codes related to hypocalcaemia.

| Read code | Code description |
|---|---|
| C354000 | Hypocalcaemia NEC |
| C354600 | Hypocalcaemic tetany |
| Q444.00 | Neonatal hypocalcaemia |
| Q444100 | Other neonatal hypocalcaemia |
| Q444111 | Hypocalcaemic tetany in newborn |
| Q444z00 | Neonatal hypocalcaemia NOS |
| Qyu6200 | [X]Other neonatal hypocalcaemia |

### *G.7.7 Identification of Read Codes Related to Seizure or Tetany*

The following truncated search terms were used to identify Read codes related to seizure or tetany: ‘seizure’, ‘fit’, ‘convul’, ‘status’, ‘tetan’. Common code stems were used to identify additional relevant codes. A total of 49 relevant codes were identified. The final list of included codes is shown in Table G.13.

**Table G.13** Read codes related to seizure or tetany.

| Read code | Code description |
|---|---|
| 1B63.00 | Had a fit |
| 1B63.11 | Fit - had one, symptom |
| 1B64.00 | Had a convulsion |
| 1B64.11 | Convulsion - symptom |
| 282..00 | O/E - fit/convulsion |
| 282..11 | O/E - a convulsion |
| 282..12 | O/E - a fit |
| 282..13 | O/E - a seizure |
| 2822.00 | O/E - grand mal fit |
| 2823.00 | O/E - petit mal fit |
| 2824.00 | O/E - focal (Jacksonian) fit |
| 2824.11 | O/E - Jacksonian fit |
| 2824.12 | O/E - focal fit |
| 2825.00 | O/E - psychomotor fit |
| 2828.00 | Absence seizure |
| 282Z.00 | O/E - fit/convulsion NOS |
| F132z12 | Myoclonic seizure |
| F250200 | Epileptic seizures - atonic |
| F250300 | Epileptic seizures - akinetic |
| F251200 | Epileptic seizures - clonic |
| F251300 | Epileptic seizures - myoclonic |
| F251400 | Epileptic seizures - tonic |
| F251600 | Grand mal seizure |
| F252.00 | Petit mal status |
| F253.00 | Grand mal status |
| F253.11 | Status epilepticus |
| F254500 | Complex partial epileptic seizure |
| F255600 | Simple partial epileptic seizure |
| F25H.00 | Generalised seizure |
| F25X.00 | Status epilepticus, unspecified |
| F25y300 | Complex partial status epilepticus |
| Fyu5200 | [X]Other status epilepticus |
| Fyu5900 | [X]Status epilepticus, unspecified |
| Q480.00 | Convulsions in newborn |
| Q480.11 | Fits in newborn |
| Q480.12 | Seizures in newborn |
| R003.00 | [D]Convulsions |
| R003100 | [D]Convulsions, infantile |
| R003200 | [D]Fit |
| R003211 | [D]Fit (in non epileptic) NOS |
| R003y00 | [D]Other specified convulsion |
| R003z00 | [D]Convulsion NOS |
| R003z11 | [D]Seizure NOS |
| Ryu7100 | [X]Other and unspecified convulsions |
| C354600 | Hypocalcaemic tetany |
| Q444111 | Hypocalcaemic tetany in newborn |
| R017.00 | [D]Tetany |
| R017000 | [D]Carpopedal spasm |
| R017z00 | [D]Tetany NOS |

### *G.7.8 Identification of Read Codes Related to Numbness or Paraesthesia*

The following truncated search terms were used to identify Read codes related to numbness or paraesthesia: ‘numb’, ‘paraesthes’, ‘tingl’, ‘needle AND pin’. Common code stems were used to identify additional relevant codes. A total of 13 relevant codes were identified. The final list of included codes is shown in Table G.14.

**Table G.14** Read codes related to numbness or paraesthesia.

| Read code | Code description |
|---|---|
| 1B41.00 | Has pins and needles |
| 1B43.00 | Has tingling sensation |
| 1B44.00 | Has numbness |
| 1B44200 | Numbness of limbs |
| 1B46.00 | C/O paraesthesia |
| 1B47.00 | Transient paraesthesia |
| 29B5.00 | O/E - paraesthesia present |
| 29B5000 | O/E - paraesthesia in hands |
| 2G2D.00 | Numbness of hand |
| G73y600 | Acroparaesthesia - unspecified |
| R020300 | [D]Tingling of skin |
| R020600 | [D]Numbness |
| R020700 | [D]Paraesthesia |

### *G.7.9 Identification of Read Codes Related to Abnormal Gait*

The following truncated search term was used to identify Read codes related to abnormal gait: ‘gait’. Common code stems were used to identify additional relevant codes. A total of 5 relevant codes were identified. The final list of included codes is shown in Table G.15.

**Table G.15** Read codes related to abnormal gait.

| Read code | Code description |
|---|---|
| 2995.00 | O/E - waddling gait |
| 299Z.00 | O/E - gait NOS |
| R012.00 | [D]Gait abnormality |
| R012z00 | [D]Gait abnormality NOS |
| Ryu3200 | [X]Other and unspecified abnormalities of gait and mobility |

### *G.7.10 Identification of Read Codes Related to Muscle Weakness*

The following truncated search terms were used to identify Read codes related to muscle weakness: ‘weak’, ‘myopathy’, ‘musc’, ‘power’. Common code stems were used to identify additional relevant codes. A total of 5 relevant codes were identified. The final list of included codes is shown in Table G.16.

**Table G.16** Read codes related to muscle weakness.

| Read code | Code description |
|---|---|
| 1B3..12 | Weakness symptoms |
| 1B32.00 | Weakness present |
| 2832.12 | O/E - weakness |
| 29A2.00 | O/E - muscle power reduced |
| F397.00 | Proximal myopathy |

### *G.7.11 Identification of Read Codes Related to Delay in Motor Development*

The following truncated search terms were used to identify Read codes related to delay in motor development: ‘motor’, ‘delay’, ‘development’’, ‘milestone’, ‘walk’, ‘sitting’, ‘crawl’, ‘stand’, ‘roll’. Common code stems were used to identify additional relevant codes. A total of 8 relevant codes were identified. The final list of included codes is shown in Table G.17.

**Table G.17** Read codes related to delay in motor development.

| Read code | Code description |
|---|---|
| 16G..00 | Unable to stand |
| 22I3100 | Not yet walking |
| 22I3200 | Not yet sitting |
| 22I3300 | Not yet standing |
| Eu82.00 | [X]Specific developmental disorder of motor function |
| R034700 | [D]Gross motor development delay |
| R034711 | [D]Gross motor skills development delay |
| R034D00 | [D]Motor delay |

### *G.7.12 Identification of Read Codes Related to Cardiomyopathy*

The following truncated search term was used to identify Read codes related to cadiomyopathy: ‘cardiomyop’. Common code stems were used to identify additional relevant codes. A total of 11 relevant codes were identified. The final list of included codes is shown in Table G.18.

**Table G.18** Read codes related to cardiomyopathy

| Read code | Code description |
|---|---|
| G55..00 | Cardiomyopathy |
| G554.00 | Other primary cardiomyopathies |
| G554400 | Primary dilated cardiomyopathy |
| G554z00 | Other primary cardiomyopathy NOS |
| G557.00 | Nutritional and metabolic cardiomyopathies |
| G557z00 | Nutritional and metabolic cardiomyopathy NOS |
| G55y.00 | Secondary cardiomyopathy NOS |
| G55y.11 | Secondary dilated cardiomyopathy |
| G55z.00 | Cardiomyopathy NOS |
| Gyu5P00 | [X]Other cardiomyopathies |
| Gyu5S00 | [X]Cardiomyopathy in nutritional diseases CE |